

Harvard Medicine

WINTER 2017

In This Together
How medicine relies
upon connections

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From the Dean



THESE EARLY MONTHS as dean of HMS have been filled with many firsts. It is especially meaningful to me that the theme of my inaugural issue of *Harvard Medicine* is connections.

I'm energized by the power that connection brings to our campus. It is central to the research conducted by our scientists; to the education provided to our medical, graduate, and postdoctoral students; and to the care provided by our clinicians. Fostering and advancing these associations among members of our community will be a priority for me.

Over the decades I have had the privilege of working with more than eighty graduate students, postdocs, and visiting scientists in my lab. Of those, nearly 80 percent now have their own trainees. Many have contributed research pivotal to the world's knowledge base and are teaching or delivering compassionate care.

The connections we build with our trainees produce meaningful legacies. At the recent gathering that marked the start of my tenure, Eugene Koh '03, the first graduate student I trained in my lab, attended as did dozens of my current postdocs and grad students. Also in attendance was Lloyd Axelrod '67, one of my clinical mentors from Massachusetts General Hospital, and other professors who have influenced my career as a physician and a scientist.

This commitment to mentoring flourishes on our campus and has been amplified by changes to our curriculum. Third- and fourth-year students now have more time to focus on mentored scholarly projects.

This time is well used. Students have worked with our faculty to investigate the molecular underpinnings of neurodevelopmental disorders. They've launched programs to assist military veterans who suffer from PTSD and to support LGBT youth. They've founded student-faculty collaborative clinics and pioneered health policy initiatives to help communities rebuild after conflicts. Recently, research by Aswin Sekar '16 led to a revolutionary theory on the genetic origins of schizophrenia. Based on the hundreds of emails to his mentor, Steve McCarroll, that news was welcomed by scientists and by families of those affected by the disease. These are reminders of how important it is to mentor our students: they advance science, they help patients, and they will, in turn, mentor those who follow them.

Our passion for discovery, teaching, and mentoring plays out in how we work together, learn from each other, and shape the future of our profession. In this issue of *Harvard Medicine*, we present some of the stories of how we connect and how our connections change the world. I look forward to sharing more stories with you in the years ahead.

A handwritten signature in dark ink, reading "G. Q. Daley".

George Q. Daley
Dean of Harvard Medical School

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Letter to the Editor

CHART NOTES FROM OUR READERS

By the Rules

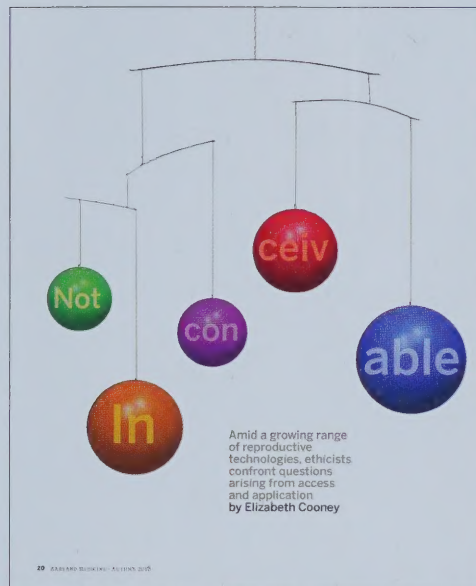
Elizabeth Cooney's article on the bioethics of reproductive technology in the Autumn 2016 issue of *Harvard Medicine* is lively and thorough. One quote, apparently referring to the clinical practice of fertility therapy, particularly drew our attention: "It is pretty much the Wild West here with unregulated opportunities to shop for someone who will help you become a parent."

From our perspective this is not an accurate representation of the highly regulated field of fertility therapy in the United States.

Clinicians practicing reproductive endocrinology and infertility have seven years of postmedical-school training, are board certified, annually maintain their board certification, and generally practice using the guidelines of the American Society for Reproductive Medicine.

All in vitro fertilization clinics operating in the United States are regulated by the Fertility Clinic Success Rate and Certification Act of 1992. IVF laboratories in the United States are accredited and regulated by bodies such as the American College of Pathologists or the Joint Commission on Accreditation of Health Care Organizations. The outcomes of IVF cycles are reported to the Society for Assisted Reproductive Technology and the Centers for Disease Control and Prevention with practice-specific statistics available to the public online.

Many IVF programs have independent ethics committees to help in making decisions about difficult situations. At our institution, for example, an assisted reproductive technologies ethics committee meets regularly and has been in existence for more than 30 years. The specialists in this field continually strive to improve their practice. Based on direct observation and our leadership roles in this specialty, we can attest



U.S. fertility practice is not lawless. It is highly professional and ethical.

ROBERT L. BARBIERI '77
BOSTON, MASSACHUSETTS

that fertility clinicians work diligently to advance the field in the service of patients.

"The Wild West" is slang for a lawless place or situation. From our perspective, U.S. fertility practice is not lawless. It is highly professional and ethical.

ROBERT L. BARBIERI '77
HMS KATE MACY LADD PROFESSOR OF
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ETHICS

Louise King shakes her head as she considers her title at the HMS Center for Bioethics: director of reproductive ethics. Who, she asks, could presume to direct such a multidimensional field? ■ A recent morning at Beth Israel Deaconess Medical Center offers a glimpse into one of the field's dimensions as King, who also is an HMS assistant professor of obstetrics, gynecology, and reproductive biology at Beth Israel Deaconess, makes her way to an ethics committee discussion about a particular couple's request. As the parents of a seriously ill child, the couple hoped for assistance in selecting an embryo that would become the best match for their child, who, barring a bone marrow transplant from a compatible donor, had a poor prognosis. In short, they wanted help conceiving a "savior sibling."

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Harvard Medicine welcomes letters to the editor. Please send letters by mail (Harvard Medicine, 107 Avenue Louis Pasteur, Suite 111, Boston, MA 02115); fax (617-432-0446); or email (harvardmedicine@hms.harvard.edu). Letters may be edited for length or clarity.



First housed at Massachusetts General Hospital, the Harvard Dental School moved to North Grove Street (pictured) in 1883.

A SHARED HISTORY

Harvard School of Dental Medicine celebrates 150 years

IN 1867, BOSTON PHYSICIAN Nathan Cooley Keep, Class of 1827, realized his bold idea, one that would forever link dentistry and medicine—and raise the bar for dental education. In the mid-nineteenth century, dentistry was largely a trade that required no formal education, and its practitioners focused on extracting decayed and damaged teeth and plugging cavities. Keep, however, viewed oral health as vital to the health of the whole body and was determined to distinguish dentistry as a branch of medicine.

His determination paid off. On July 17, 1867, Harvard President

Thomas Hill confirmed a resolution put forward by Keep and HMS faculty to establish Harvard Dental School, the nation's first dental school connected to a university and its medical school. It was also the first U.S. dental school to confer the *Dentariae Medicinae Doctoris* degree, a designation that emphasized students' medical training. Keep served as the dental school's first dean, his name forever honored on the school's shield by the central placement of a castle keep.

The five students who made up the school's inaugural class included Robert Tanner Freeman,

a son of former slaves. Keep had encouraged Freeman to apply to Harvard, and had, in fact, successfully petitioned for an end to the college's exclusion of Blacks and other ethnic minorities. In 1869, Freeman became the first Black to graduate from Harvard Dental School and is believed to be the first Black in the country to earn a degree in dentistry. A year later, George Franklin Grant graduated from the dental school and went on to become the first Black faculty member of Harvard University and of the dental school.

Harvard Dental School, renamed Harvard School of Dental Medicine in 1940, quickly earned an international reputation for its high standards and thorough professional training in dentistry. Its faculty are part of the Faculty of Medicine, a united faculty from both schools, underscoring the important relationship between dentistry and medicine.

One hundred fifty years after its founding, the connection between the dental and the medical schools remains strong. Dental students spend the first year of their education attending the same classes as their medical school peers. Today's students also learn how oral health and primary care integrate through rotations in the Teaching Practices of the Harvard Dental Center, the only clinical facility within a Harvard graduate school to provide direct patient care. True to Keep's vision, the students gain an intellectual experience that reflects the biological underpinnings of oral and systemic health, the value of evidence-based research, and the importance of clinical study. —Heather Denny



Wheels of Life

The Family Van marks a quarter century of service

FOR THE PAST 25 YEARS, the Family Van has been a successful model for the direct delivery of health care and preventive medicine.

The Family Van's mission to bridge the gap between low-income communities and access to health care has remained its guiding light since its founding. People who visit the van as it travels through Dudley Square and other Boston neighborhoods near the Longwood campus are screened and coached on ways to develop healthy habits that can help reduce health concerns such as high blood pressure or cholesterol levels.

Since its inception, the program has provided preventive services for an estimated 63,000 people. About a quarter of those who have visited the van first learned that they were at risk for one or more chronic illnesses such as diabetes, hypertension, or HIV. According to research conducted by Family Van cofounder Nancy Oriol '79 and others, the mobile health care unit's services have also led to consid-

erable cost savings by local emergency departments.

"In 1992," says Oriol, HMS faculty associate dean for community engagement in medical education and an HMS associate professor of anaesthesia at Beth Israel Deaconess Medical Center, "Cheryl Dorsey '91, then a third-year HMS student, and I spent a year codesigning the Family Van with our Boston neighbors. We created our program to be a visible symbol of health as a valued family tradition and of trust as a valued medical tradition. We have now made more than 100,000 deliveries of health care directly to streets where our families live, work, learn, and play. It's been magical."

The Family Van continues to serve these communities, especially those that are most at risk. The program also works with nearly one hundred partners, including health centers, community and housing development organizations, and food pantries, to address other unmet needs that may affect their patients' health.

Inside View

Cryo-electron microscopy center set to transform biomedical imaging at HMS

A COLLABORATION OF PARTNERS from HMS, Harvard University's Office of the Provost, Boston Children's Hospital, and Dana-Farber Cancer Institute has led to the creation of the Harvard Cryo-Electron Microscopy Center for Structural Biology in the Longwood Medical Area. The cryo-electron microscopes that will make up the center's technology infrastructure will allow scientists to see molecules from a perspective that could lead to a better understanding of molecular mechanisms in both normal and disease states and to the development of next-generation precision therapeutics.

George Q. Daley '91, dean of HMS, said, "We now have a microscope that allows us to see single molecules at the atomic level. This innovation will energize science in the hospitals and on the Quad, catalyzing translational research to see where it can bear on disease."

Said Alan Garber, provost of Harvard University, "This new center demonstrates how Harvard and its affiliated institutions can partner to establish leading-edge facilities and resources that accelerate biomedical discoveries."

Stephen Blacklow '88, the Gustavus Adolphus Pfeiffer Professor of Biological Chemistry and Molecular Pharmacology and chair of the department of at HMS, remarked, "The cooperation and resolve shown by all participants in pursuit of this effort has been truly impressive and foreshadows an outstanding future for molecular visualization at Harvard."

Cryo-electron microscopy (cryo-EM) represents the latest frontier in imaging deployed by structural biologists.

The technique of X-ray diffraction, famously used to produce patterns from DNA that helped scientists glean its structure, stimulated the field of molecular biology. The structure showed how DNA could carry the genetic code. Since that time, X-ray crystallography and nuclear magnetic resonance have become the standard approaches used by structural biologists to visualize molecules at atomic resolution.

Cryo-EM has begun to challenge those methods for the analysis of large molecules assembled in specific configurations. Researchers are using advanced cryo-EM methods to reveal the minute details of the structures of proteins and protein complexes. Seeing distinct functional states affords a deeper understanding of how the molecular machines of a cell operate.

The new center at HMS will be directed by Stephen Harrison, the Giovanni Armenise-Harvard Professor of Basic Biomedical Science in the Department of Biological Chemistry and Molecular Pharmacology at HMS.



Filarial worm that causes river blindness

Star Power

Ingestible capsule could deliver medicine for two or more weeks

IMAGINE SWALLOWING A PILL designed to release a daily dose of medication for an entire week, month, or even longer. That idea may soon be a reality; HMS investigators at Brigham and Women's Hospital together with colleagues at MIT have developed just such a drug-delivery capsule. Their report appears in the November 16, 2016, issue of *Science Translational Medicine*.

The researchers developed a prototype that is about the size of a fish-oil capsule. Once

inside the stomach, the capsule unfolds into a star-shaped structure. Although the size of the device prevents it from passing through the pylorus and exiting the stomach, it will allow food to pass through the digestive system.

The team used both mathematical and animal models to investigate the effects of using the capsule to deliver a sustained therapeutic dose of ivermectin, which is used to treat parasitic infections such as river blindness and has been found to keep malaria-carrying mosquito populations at bay. The team found that in large-animal models the capsule remained in the stomach and slowly released the drug for up to 14 days.

"The gastrointestinal tract is a strong, durable passageway through the body," says C. Giovanni Traverso, an HMS instructor of medicine, gastroenterologist and biomedical engineer at Brigham and Women's, and co-corresponding author of the study. "We designed the capsule to pause its transit in the stomach to allow for more controlled drug delivery and absorption before passing harmlessly through the gastrointestinal tract."

The capsule contains polymers and other materials mixed with ivermectin to allow the drug to slowly diffuse over time. The team saw evidence of diffusion for up to two weeks and is interested in further developing the device so that it can dispense a drug for one month or longer.

The research was spurred by the promise of eradicating malaria and the problem of medication nonadherence. It can be difficult to remember to take medications when prescribed, so it's not uncommon for patients to stop following their medication plans. In this country alone, medication nonadherence is estimated to lead to roughly \$100 billion in medication-related hospital admissions annually.

Making Connections

Meeting patients' basic needs can improve clinical outcomes

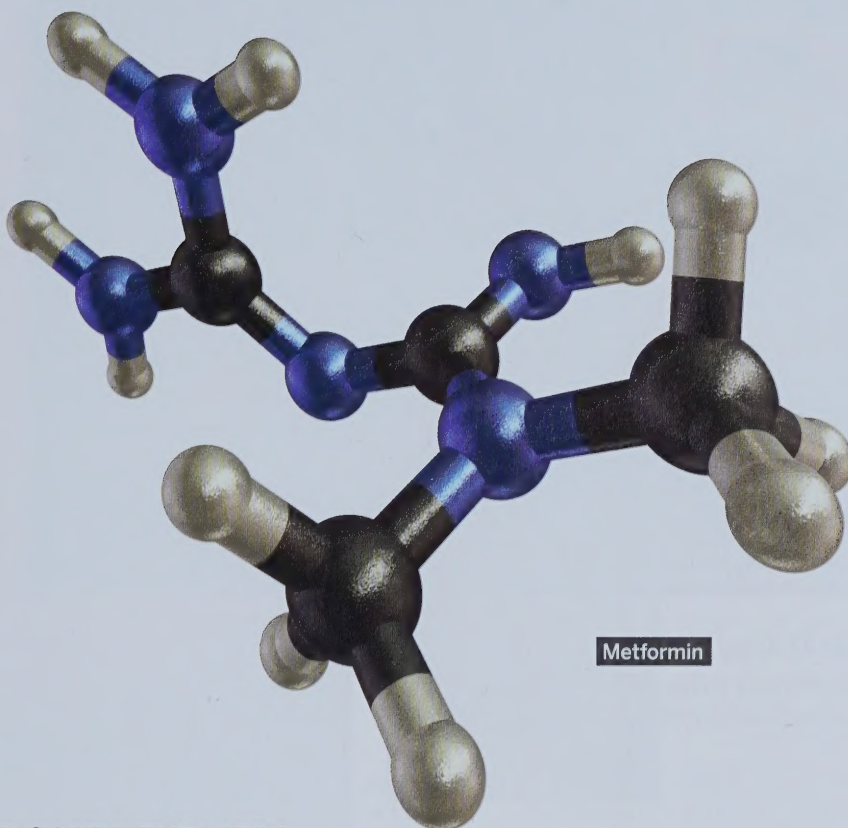
HELPING PATIENTS meet food, housing, transportation, and other socioeconomic needs can lead to modest but significant improvements in key cardiovascular risk factors such as high blood pressure and cholesterol levels, say HMS investigators at Massachusetts General Hospital, working in collaboration with Health Leads, a Boston-based organization that helps health care delivery groups connect patients with local services.

"We know that unmet basic resource needs for things like nutritious food, housing, transportation, and medication are common and are associated with poor health outcomes," says Seth Berkowitz, an HMS instructor in medicine at Mass General and corresponding author of the report, published online on December 12, 2016, in *JAMA Internal Medicine*. "We've offered the Health Leads intervention program for the past few years, but we did not know whether this strategy for addressing patients' unmet needs would lead to changes in clinical outcomes."

Primary care patients seen at three Mass General primary care practices from October 2013 through April 2015 were surveyed for their interest in assistance with paying for healthy food, prescription medicine, or utility bills; finding a job; or securing housing or other financial help.

Of more than 5,000 screened patients, nearly 2,000 had at least one unmet need. About 60 percent of that group agreed to enroll in the Health Leads program. Based on a review of medical records for all screened patients—those with unmet needs who enrolled in Health Leads, those with unmet needs who did not enroll in Health Leads, and those who declined services—Health Leads participants with hypertension had greater reductions in both systolic and diastolic blood pressure than did patients with hypertension who were not enrolled in Health Leads.

Participants with elevated LDL cholesterol levels who enrolled in Health Leads also saw greater improvement. No significant differences, however, were seen in the glycated hemoglobin (HbA1c) levels of Health Leads participants with diabetes. —Sue McGreevey



Metformin

DOUBLE DUTY

Gene pathway could block cancer cell growth, support healthy aging

ALTHOUGH CONSIDERABLE EVIDENCE shows that the drug metformin, used for more than 50 years to treat type 2 diabetes, can prevent or slow the growth of certain cancers, the mechanism behind these anticancer effects has been unknown. Recently, however, a team of HMS researchers at Massachusetts General Hospital has identified a pathway that appears to underlie metformin's ability to both block the growth of human cancer cells and extend the lifespan of the roundworm *Caenorhabditis elegans*, findings indicating that this single genetic pathway plays an important role in a wide range of organisms.

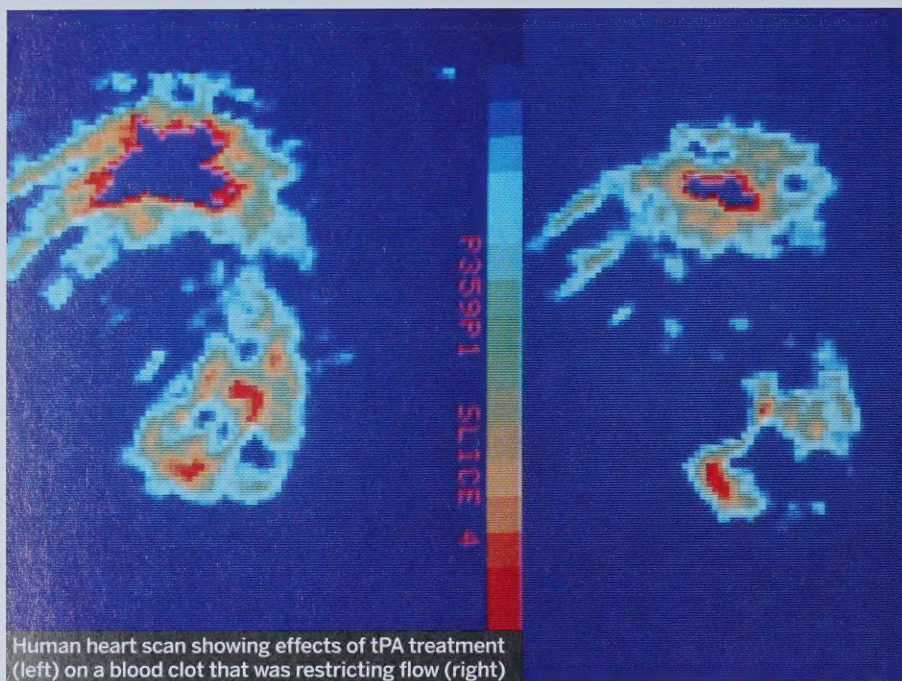
"We found that metformin reduces the traffic of molecules into and out of the cell's nucleus," says Alexander Soukas, an HMS assistant professor of medicine and senior author of the paper published in the December 15, 2016, issue of *Cell*. "Reduced nuclear traffic translates into the ability of the drug to block cancer growth. Remarkably, this reduced traffic is also responsible for metformin's ability to extend lifespan."

Metformin helps lower blood glucose in patients with type 2 diabetes by reducing the liver's ability to produce glucose for release into the bloodstream, possibly by blocking the activity of mitochondria, structures that fuel cellular activity.

Soukas and colleagues found that metformin's action against breast, prostate, and pancreatic cancers relies on two elements of a single genetic pathway—the nuclear pore complex—which allows the passage of molecules into and out of the nucleus, and an enzyme called ACAD10.

"Our experiments showed two important things," says Soukas, who is also a faculty member of the Mass General Center for Genomic Medicine. "If we force the nuclear pore to remain open or if we permanently shut down ACAD10, metformin can no longer block the growth of cancer cells. That suggests that the nuclear pore and ACAD10 may be manipulated in specific circumstances to prevent or even treat certain cancers."

—Sue McGreevey



Human heart scan showing effects of tPA treatment (left) on a blood clot that was restricting flow (right)

Break It Up, Now

Approach may offer potential for safer, more effective removal of blood clots

THE STANDARD OF CARE for treating strokes caused by blood clots involves the therapeutic infusion of tissue plasminogen activator (tPA), which can help dissolve the clots and restore blood flow. This thrombolytic treatment carries the risk of bleeding and swelling in the brain and must be administered within three hours from the start of the stroke, which sharply limits its clinical benefits.

Researchers at Joslin Diabetes Center have now demonstrated in animal models the potential of giving a drug that targets a coagulation factor in combination with tPA. The combination might improve stroke outcomes and increase the window of opportunity for the therapy. The study was reported online on January 27 in the journal *Blood*.

Drugs that target the proteins plasma kallikrein and factor XII, which promote coagulation, “may provide the opportunity to make tPA safer by reducing these complications and increasing its efficacy in opening blood vessels,” says Edward Feener, an HMS associate professor of medicine at Joslin and study co-author. About 800,000 people in the United States suffer a stroke each year, and about 87 percent of those strokes are

ischemic, in which blood flow is blocked by a clot.

The research team first demonstrated that tPA boosts the activity of plasma kallikrein in both human and mouse plasma. They then looked at mouse models in which blood clots had been induced in the brain and then treated with tPA and a plasma kallikrein inhibitor. The animals that were genetically modified to produce lower amounts of plasma kallikrein showed significantly less bleeding, brain swelling, and damaged brain areas than control animals without a plasma kallikrein blockade.

The researchers traced the biological mechanisms by which tPA activates plasma kallikrein via factor XII. Plasma kallikrein is known to activate the kallikrein-kinin system, a pathway that has been implicated in stroke complications including brain swelling and the breakdown of the blood-brain barrier.

The U.S. Food and Drug Administration has approved a plasma kallikrein inhibitor for the treatment of hereditary angioedema. These new findings suggest additional potential therapeutic opportunities for plasma kallikrein inhibitors in thrombolytic therapy.

METAL PATCH

Exploring zinc chelation to regenerate injured optic nerves

FOR MORE THAN TWO DECADES, researchers have tried to regenerate injured optic nerves using different growth factors or agents that overcome natural growth inhibition. They’ve had partial success, sometimes even restoring rudimentary elements of vision in mouse models.

At best, the methods resulted in about only 1 percent of the injured nerve fibers regenerating and reconnecting the retina to the brain. That’s because most of the damaged cells, known as retinal ganglion cells, eventually die, says Larry Benowitz, an HMS professor of neurosurgery at Boston Children’s Hospital.

Benowitz and colleagues have found a surprising approach that gets these ganglion cells to live longer and regenerate robustly: use chelating agents to bind the zinc that’s released as a result of the injury.

These studies were done in mice. If the findings hold up in humans, they could be used for people with optic nerve injury as a result of trauma, glaucoma, or other causes, and possibly even in people with spinal cord injury, the researchers say. The results were published online on January 3 in *Proceedings of the National Academy of Sciences*.

Zinc release is normally tightly controlled, because high levels are toxic to cells. But the research team found that within an hour after injury to the optic nerve, zinc levels spiked, not in the damaged retinal ganglion cells themselves but in cells that “talk” to them, interneurons known as amacrine cells.

Two or three days later, when the zinc transferred to the retinal ganglion cells, the cells began to die.

“When we used zinc chelators, we enabled about 40 percent of the injured cells to survive for months and possibly indefinitely,” says Benowitz. “Growth factors and survival factors only have a transient effect; they don’t really stop the cell death process. If you hit the right dosage and deliver zinc chelators continuously, you might have half of the retinal ganglion cells surviving.”

The researchers are also interested in exploring how zinc causes cell death and blocks regeneration.

Although this is the first study to demonstrate the role of zinc in optic nerve injury, zinc has also been shown to play a role in stroke injury and has been implicated in Alzheimer’s disease and amyotrophic lateral sclerosis.

—Nancy Fliesler



Diabetic retinopathy

Just a Dash

Growth factor shown to protect the retina in early stage diabetes

INTRODUCING A SMALL INCREASE in transforming growth factor beta (TGF- β) into the eyes of animals with diabetic eye disease has been found to protect against diabetic retinopathy, which damages retinal blood vessels during the early stages of diabetes. The discovery, by HMS researchers from the Schepens Eye Research Institute of Massachusetts Eye and Ear, was reported online February 2 in the *American Journal of Pathology*. The research team says the findings may lead to targeted therapeutics that delay or prevent the development of the disease in patients.

"We found that increased TGF- β is really defending the vessels in the retina," says senior author Mara Lorenzi, an HMS professor of ophthalmology, emerita; a recently retired senior scientist at Schepens; and the study's senior author. "When we took away the small increase in TGF- β , we saw significant damage to the retinal vessels in animals with diabetes. Based on this finding, we'd now like to know if a little extra TGF- β will help protect the retinal vessels in patients with diabetes."

Diabetic retinopathy, the most common diabetic eye disease and a leading cause of blindness in adults in this country, occurs when blood vessels in the retina become damaged and leak fluid. As the fluid builds up, the retina can swell, and retinal vessels become blocked and can no longer carry blood. New blood vessels grow on the surface of the retina but can leak or rupture, impairing vision. Currently, there are no treatments for diabetic retinopathy beyond controlling blood glucose and blood pressure levels.

Based on this finding, the study authors not only warn against the use of TGF- β blocking as a therapy for diabetes-related damage to kidneys and other body parts, but also suggest that there may be ways to identify drugs for upward modulation of TGF- β signaling in a very controlled fashion to prevent or delay diabetic retinopathy.

—Suzanne Day

Signposts

Serum microRNAs may serve as biomarkers for multiple sclerosis



Cervical vertebrae scan showing multiple sclerosis

THE SMALL RNA molecules known as microRNAs, which influence basic cellular processes, may be long-awaited biomarkers for the diagnosis, progression, and treatment of multiple sclerosis, according to findings from a study conducted by HMS researchers at the Ann Romney Center for Neurologic Diseases at Brigham and Women's Hospital.

In research that appeared online January 23 in *JAMA Neurology*, serum microRNAs were

linked to MRI findings in the brain and spinal cord in patients with multiple sclerosis. These findings suggest that microRNAs could serve as biomarkers for monitoring the progression of the disease and for identifying distinct underlying disease processes, such as inflammation and tissue destruction.

The researchers examined the connection between serum microRNAs and MRI measures taken to evaluate the severity of patients' disease. This included looking at lesions and atrophy, an indication of degeneration of the cells in the central nervous system. The research team found that the expression of certain microRNAs was linked to the MRI measures. They also found that different mechanisms were linked to different locations of disease-related changes, such as in the brain or spinal cord. Additionally, the findings suggested that certain sets of microRNAs were linked to lesions, while others were linked to atrophy, which is known to have more devastating effects.

"These findings tell us the disease is heterogeneous. There's a complex set of mechanisms at play, and it may vary from patient to patient," says senior co-author Rohit Bakshi, the HMS Jack, Sadie and David Breakstone Professor of Neurology at Brigham and Women's and an HMS professor of radiology at the hospital. "Another implication of this research is that it could eventually lead to us having a blood test to identify the subtype of multiple sclerosis in a patient and help guide therapeutic decisions and prognosis."



Dopamine-producing cell used in research on Parkinson's disease

Rest and Recoup

Posture-mediated low blood pressure could mask cognitive deficits in Parkinson's

A RESEARCH TEAM made up of HMS neurologists at Beth Israel Deaconess Medical Center and neuropsychologists at Boston University has found that when patients with Parkinson's disease experience a drop in blood pressure upon standing up—a condition known as orthostatic hypotension—they also exhibit significant cognitive deficits. These deficits reverse when patients lie down and their blood pressure returns to normal. These findings were reported on January 3 in *Neurology*.

Although these cognitive impairments can go unnoticed by physicians assessing patients with Parkinson's who are lying down or seated, the impairments could lead to difficulty in daily activities performed while standing and walking, such as tracking conversations, counting change, and interpreting traffic signals.

Marked by characteristic tremor, rigidity, and slowness of movement, Parkinson's disease is a progressive degeneration of parts of the nervous system. It affects many aspects of movement and can cause a masklike, expressionless face; rigid limbs; and problems with walking and posture. Parkinson's is also associated with cognitive defects attrib-

uted to breakdowns in connectivity between regions of the brain. Up to 50 percent of people with Parkinson's disease may also have orthostatic hypotension (OH).

The research team divided fifty-five volunteers into three study groups: eighteen patients with both Parkinson's and OH, nineteen patients with Parkinson's but without OH, and eighteen control participants with neither Parkinson's nor OH.

When the three groups' relative performances were compared with each other, participants with both Parkinson's and OH were far more susceptible to posture-related impairment on several tests, including those that measured math skills and abilities such as producing words easily, keeping information in mind while working on it, paying sufficient attention so that later memory is efficient, and searching for items quickly and accurately.

"Based on the results of this study," says co-senior author Roy Freeman, an HMS professor of neurology and director of the Center for Autonomic and Peripheral Nerve Disorders at Beth Israel Deaconess, "we encourage clinicians to include cognitive testing in a variety of postures in their assessments of patients." —Jacqueline Mitchell

Food Court

Link between intestinal microorganisms, diet, and colorectal cancer strengthens

MICROORGANISMS LIVING IN THE LARGE INTESTINE have been suspected as a link between diet and certain types of colorectal cancer, but now a study by HMS researchers at Dana-Farber Cancer Institute and Massachusetts General Hospital provides the strongest evidence to date that this is true.

The paper, published online on January 26 in *JAMA Oncology*, focuses on *Fusobacterium nucleatum*, one of hundreds of types of bacteria that dwell in humans' large intestines and one thought to play a role in colorectal cancer. By tracking the diets of more than 137,000 people for decades and examining more than 1,000 colorectal tumor samples for *F. nucleatum*, the researchers determined that individuals following a "prudent" diet, that is, one rich in whole grains and fiber, had a lower risk of developing types of colorectal cancer containing the bacterium. Their risk for colorectal cancer types that lacked the bacterium, however, was essentially unchanged.

"Though our research dealt with only one type of bacteria, it points to a much broader phenomenon—that intestinal bacteria can act in concert with diet to reduce or increase the risk of certain types of colorectal cancer," says Shuji Ogino, an HMS professor of pathology at Dana-Farber, professor of epidemiology at the Harvard T.H. Chan School of Public Health, and co-senior author of the study.

The research drew on dietary records of participants in the Nurses' Health Study and Health Professionals Follow-up Study, both large-scale health-tracking studies. Some of the participants had developed colon or rectal cancer over decades. The researchers measured the levels of *F. nucleatum* in the patients' tumor tissue and merged these data with information on diet and cancer incidence.

Participants who followed a prudent diet had a lower risk of developing colorectal cancer laden with *F. nucleatum*. But they received no extra protection against colorectal cancers that didn't contain the bacteria.

The authors note that the study results underscore the need for research that further explores the complex interrelationship between what someone eats, the microorganisms in their gut, and the development of cancer.





C CHANGE

Quality improvement efforts
lower rates of cesarean deliveries

INTERVENTIONS AIMED at lowering the rate of cesarean deliveries have resulted in a significant reduction in such deliveries over a seven-year study period at Beth Israel Deaconess Medical Center, according to HMS clinician-researchers at the hospital. The study appeared in the February issue of *The Joint Commission Journal on Quality and Patient Safety*.

Nearly one in three babies born in the United States is delivered via cesarean section, or C-section. Compared to vaginal delivery, cesareans are associated with a number of increased health risks for mother and baby including increased mortality and longer hospital stays, and increased health care costs. The study measured the impact of a series of strategic quality improvement interventions on the hospital's nulliparous term singleton vertex (NTSV) cesarean rate, or the proportion of single babies carried to at least 37 weeks in the vertex position born to women having their first baby that was delivered via cesarean.

"The rate of cesarean deliveries in low-risk women varies significantly from hospital to hospital across the nation, and such wide dispari-

ties suggest that some cesarean deliveries may be performed for reasons other than medical necessity," says Mary Vadnais, an HMS instructor in obstetrics, gynecology and reproductive biology, part-time, a maternal-fetal medicine specialist, and vice chair of the Quality Assurance Committee/Obstetrics at Beth Israel Deaconess, and first author on the study.

Beginning in 2008, Beth Israel Deaconess obstetricians implemented a series of interventions in five areas: interpretation and management of fetal heart-rate tracings, provider tolerance for labor, induction of labor, provider awareness of NTSV cesarean delivery rates, and environmental stress. During the intervention period, researchers found that the NTSV cesarean rate decreased from nearly 35 percent to a fraction over 21 percent, which is below the U.S. Department of Health and Human Services' recommended target rate of 23.9 percent. The hospital's overall cesarean rate also declined from 40 percent to 29 percent over the same period.

Vadnais and colleagues used published data and assessed environmental factors in

the Beth Israel Deaconess labor and delivery unit to design strategic interventions aimed at lowering the NTSV cesarean delivery rate. In some cases, these interventions meant standardizing protocols, increasing provider education, or revising guidelines. For example, slow progression of labor is a common reason for cesarean delivery. Historical norms for labor progress, however, may not apply to modern obstetrical populations. Reassessing how to manage slower labors allowed physicians to avoid cesarean deliveries based solely on the previously expected rate of cervical changes.

A recognized association exists between a hospital's environmental factors and its cesarean delivery rate. To optimize the environment at the hospital, the labor and delivery unit conducted emergency cesarean delivery drills to strengthen cohesiveness between the provider and unit staff members, increasing the unit's ability to support the physician during an urgent situation. The department also created more flexible visitor guidelines to promote continual emotional support for the patient.

—Emily Barrett



Hair cells treated with gene delivered by virus carrier

LISTEN UP

New gene-delivery therapy restores partial hearing, balance in murine model

USING A NOVEL FORM OF GENE THERAPY, scientists at HMS and Massachusetts General Hospital have managed to restore partial hearing and balance in mice born with a genetic condition that affects both.

The model overcomes a long-standing barrier to accessing hair cells, the delicate sensors in the inner ear that capture sound and head movement and convert them to neural signals for hearing and balance. The findings appeared in the February issue of *Molecular Therapy*.

Although the approach is years away from use in humans, gene therapy could help restore hearing in several forms of genetic and acquired deafness. Some 30 million people in this country suffer from hearing loss, and every year, about one in 1,000 babies are born with a hearing impairment, according to the U.S. Centers for Disease Control and Prevention.

In their quest to restore hearing through gene therapy, scientists have long sought ways to improve gene delivery into hair cells.

Previous approaches were only marginally effective as they reached one set of hair cells in the inner ear, while hair cells in the outer ear—equally critical for hearing—remained largely impenetrable.

“To treat most forms of hearing loss, we need to find a delivery mechanism that works for all types of hair cells,” says neurobiologist David Corey, the Bertarelli Professor of Translational Medical Science at HMS and co-senior investigator on the study.

To achieve that, the researchers used adeno-associated virus (AAV), which is already used as a gene-delivery vehicle for retinal disorders but had not been effective in hair cells.

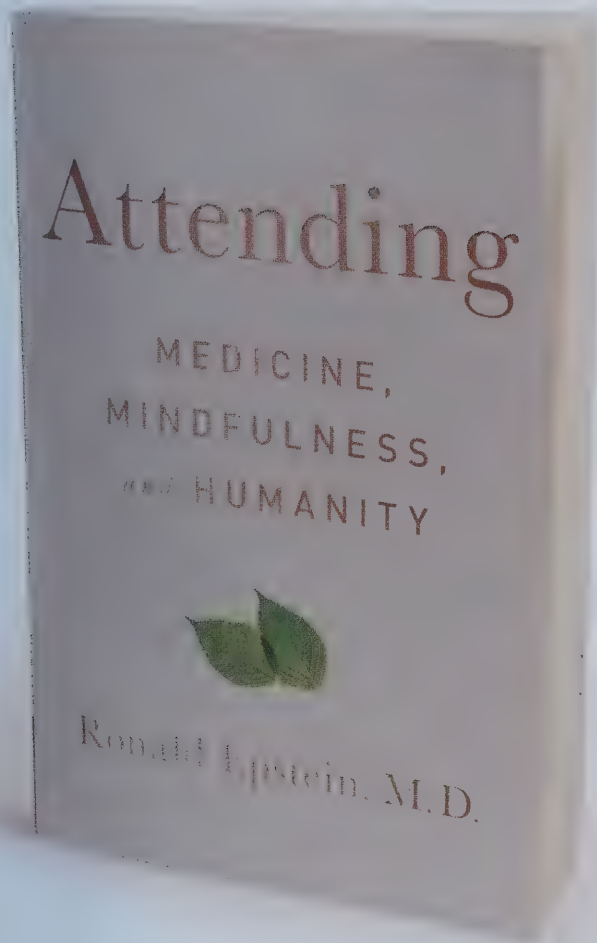
To improve the chances of delivery into the hair cells, the team wrapped a form of AAV in cell-membrane bubbles called exosomes, an approach recently developed by study co-senior author Casey Maguire, an HMS assistant professor of neurology at Mass General, and research team member Xandra Breakefield, an HMS professor of neurology at Mass General. The membrane wrapping the virus is coated with proteins that bind to cell receptors. This protein coat may help the bubble-wrapped form of AAV, or exo-AAV, effectively bind to and penetrate the hair cells, says Maguire.

In lab dish experiments, exo-AAV penetrated 50 to 60 percent of hair cells, the researchers observed; AAV alone penetrated only 20 percent of the cells.

The researchers tested the approach in mice born without a gene critical for hair cell function. Such animals normally cannot hear even the loudest sounds and exhibit poor balance. Post-treatment tests revealed that the gene entered between 30 and 70 percent of hair cells and reached both inner and outer ear hair cells.

A month after treatment, nine of twelve mice had some level of hearing restored and could be startled by a loud clap, a standard behavioral test for hearing. Four could hear sounds of 70 to 80 decibel intensity, the rough equivalent of conversation in a loud restaurant. Treated mice also had notably improved balance, compared with their untreated counterparts, showing far less head tossing or running in circles, both markers of instability or disorientation.

—Elizabeth Dougherty and Ekaterina Pesheva



HEAD SPACE

Attending: Medicine, Mindfulness, and Humanity
by Ronald Epstein, MD
(SCRIBNER, 2017)

reviewed by Elissa Ely

I STARTED READING *Attending: Medicine, Mindfulness, and Humanity* after completing a 16-hour training in electronic health records. The timing was coincidental but fortunate, as despair was only a checkbox away.

Author Ronald Epstein '84—family physician, palliative care consultant, meditator, harpsichordist—has given mindfulness a great deal of thought, especially in a medical era of “demoralizing metrics that measure what can be counted and not what really counts.” *Medicine and meditation*, he points out, derive from the same etymologic root: “to consider, advise, reflect.” (I’m compelled to note that *electronic health record* has no similar derivation.)

Most of us want to recognize and address suffering; to consider, advise, and reflect. Current medical training, Epstein argues, claims an interest in all this but “largely ignores the development of these capacities.” In spite of that, empathic master clinicians roam among us, recognizable by the kind of care they give. These doctors use analytic and imaginative thinking in tandem in order to “cultivate ... informed intuition” and “transform ... discomfort into curiosity.”

For instance, up to a third of patient symptoms ultimately defy diagnosis (blowing the “minds” of EMR programs, which don’t permit notes to be signed without billable International Classification of Diseases codes). Curiosity trumps what Epstein calls “the tyranny of categories,” and attentiveness trumps the kind of obedient enervation that leads to burnout. He describes a chart he once read with checks in all the required boxes: smoking habits, alcohol use, risky sexual behavior. The patient was a six-month-old baby.

We know the benefits of treating haste and stress in our patients—prescribing mindfulness programs has become almost pro forma—but we remain less rigorous about treating them in ourselves. Still, possibilities exist. Along with a colleague, Epstein developed a yearlong mindful practice program for primary care physicians. Another colleague of his started a “confessions” project for anesthesiology residents: In typed, Times New Roman font, the residents anonymously submit stories of personal disasters (and, occasionally, disasters averted) and then read them aloud to one another. Instead of the traditional haze of blame, disclosure creates community. A third colleague, bowing to the inevitable, reoriented her computer so that she and her patients could view its screen together.

What does Epstein do with his own haste and stress?

“Elapsed time might be out of a doctor’s control to some degree,” he writes, “but perceived time can always be created.” Before entering each patient’s room, he pauses. His screen saver rotates through a series of poems. He meditates, of course, and encourages what the Zen masters call “beginner’s mind” in his thinking. Sometimes, when he could be modifying billing codes, he instead walks a patient in pain to and from the reception area. They don’t suffer alone.

Beginning with his book’s title, Epstein’s point is crystal clear. But to make it even clearer, he enlists the writings of other master clinicians: a Zen roshi, Niels Bohr, Bach, John Dewey, Rumi. They are thoughtful company in times when we’ve never needed thoughtful company more.

Elissa Ely '87 is a Massachusetts-based psychiatrist.



The good medicine of
gentle contact with our skin
by Elizabeth Dougherty

Soft touch

Tell a moving story and, often, the person listening will feel compelled to reach out and touch you. The simple gesture communicates understanding, empathy, and a reassurance that you are not alone. ■ Skin, our largest organ, is a powerful conveyor of connection. Yet how skin deciphers touch, discerning strokes from taps and taps from jabs and connecting these sensations to meaning and emotion, is only just beginning to be understood. ■ Touch has been notoriously challenging to study. Scientists who research visual and auditory systems have been able to selectively disable these senses in animal models as a means of penetrating how they function. But it is difficult to “disable” the skin and the sensations it propagates, so learning what happens in a system devoid of touch has been almost unattainable. ■ There is, however, a place where touch has been practically forbidden for most of the past century: neonatal intensive care units. It is in these units that the power of touch is being rediscovered.





Pablo Picasso
Mother and Child
1921
142.9 x 172.7 cm
Oil on canvas

Crowds visiting Luna Park at Coney Island, New York, in the early 1900s could purchase tickets to view infants resting in "isolettes," early versions of the incubator.



Come One, Come All

If you were strolling the Boardwalk at Coney Island in 1903, you probably would have seen this sign: Infant Incubators with Living Infants. The 25-cent admission would have allowed you to see an array of glass-doored nests. Each nest held a tiny baby tucked safe and warm within.

The doctor in charge, Martin Couney, had gathered the babies from New York hospitals that didn't have access to what Couney called "isolettes." These rudimentary incubators had been inspired by poultry-hatching systems and invented by Couney's colleagues in France, where their use had reduced the mortality rates of premature babies by 25 percent. During the nearly half-century run of his Coney Island sideshow, Couney cared for thousands of infants and saved the lives of most.

In those early days, the focus of neonatology was survival. Before the isolette, it

was hard to keep full-term infants alive, let alone those born early or underweight. The incubator changed expectations, and as the twentieth century progressed, so did the technology. Doctors invented more specialized incubators and designed ventilators suitable for the tiny lungs of premature babies. One pioneering pediatrician, Mary Ellen Avery, the first woman appointed physician-in-chief at what was then Children's Hospital Boston, discovered that preterm infants lacked a lung surfactant that helped with breathing, and she figured out how to introduce it therapeutically. Soon enough, every vital sign had a monitor, and advances in therapeutic interventions became almost commonplace.

"We wanted everything controlled, everything measured," says Terrie Inder, the HMS Mary Ellen Avery Professor of Pediatrics in the Field of Newborn Medicine at Brigham and Women's Hospital, chair of the Department of Pediatric Newborn Medicine at Brigham and Women's and a professor of pediatrics at Massachusetts General Hospi-



Terrie Inder



Grace Chan

tal. “Once we started keeping them alive, we exploded in terms of things we could do.”

In the United States today, babies born at just 22 weeks and weighing barely over a pound—about the size of a grapefruit—have a good chance of surviving. The same is not true for preterm births elsewhere, however. Each year throughout the world, 15 million babies are born early, and preterm birth is still one of the top causes of newborn deaths worldwide.

Of the preterm babies who do survive, many grow up with social and physical difficulties that range from problems with attention and social interactions to cognitive deficits and anxiety. “The preterm phenotype was well recognized,” says Inder, “but not what was causing it. It didn’t seem to be brain injury. It didn’t seem to be a drug that was given. It seemed more complex.”

Or, possibly, simpler.

Evidence being gathered by Inder, and by epidemiologists and neurobiologists, suggests that preterm babies need a nurturing touch.

Touchstone

A little more than three decades ago, an intervention called kangaroo mother care emerged in a maternity ward in Colombia. Incubators were scarce, so mothers and nurses strapped preterm babies to their chests to keep them warm. The technique improved survival.

Over the years, doctors have learned how a session of kangaroo care affects a baby physiologically: the infant’s heart rate, blood pressure, and respiration stabilize; signs of stress diminish; and an ideal body temperature is maintained.

Researchers and clinicians have continued to assess the potential benefits of this care; kangaroo mother care remains the most well-studied form of clinically defined nurturing touch. Grace Chan ’06, an HMS assistant professor of pediatrics at Boston Children’s Hospital and an epidemiologist at Harvard T.H. Chan School of Public Health, recently reviewed more than one thousand studies of this type of care, zeroing in on 124 that included mother–child skin-to-skin touch and neonatal outcome measures: Although

babies benefit from kangaroo care provided by fathers, studies tend to focus on interventions involving mothers.

Chan found that preterm and low-birth-weight babies benefited from kangaroo mother care in several ways. Their risk of infection was lower than that of similar infants without skin-to-skin care as were their body temperatures and blood-sugar levels. The infants also showed lower respiratory rates and lower pain measures than their counterparts. In addition, they grew faster, and they were more likely to succeed at breastfeeding. Perhaps most impressive was the fact that babies involved in kangaroo care were 36 percent less likely to die than those without the benefit of the program.

Not only did kangaroo care affect babies’ health, it also reduced infant readmissions to hospitals by 58 percent. Although Chan’s analysis did not find that babies given kangaroo care went home earlier than other infants, some of the studies she reviewed did report shortened stays in neonatal intensive care units.

McConnell is collaborating on an initiative that provides cash support to mothers, with the goal of seeing whether such help affects the time mothers are able to spend providing kangaroo care for their babies.



Margaret McConnell

"There's a benefit in trying to figure out how kangaroo mother care can be adopted and used more widely," says Chan.

There's also evidence that kangaroo care may have lasting effects on a baby's health and well-being, results that could address some of the concerns associated with the preterm phenotype. A study conducted at Bar-Ilan University in Ramat-Gan, Israel, and published in 2014 in

Biological Psychiatry, compared 146 premature infants: half of whom received kangaroo care for an hour a day each day for two weeks, and half who received standard incubator care. All the children in the study were evaluated repeatedly through age 10. Those who had received kangaroo care had lower levels of stress and anxiety and higher levels of cognitive development throughout that first decade.

Go Gentle

In situations where kangaroo care isn't possible—when a parent isn't available or a baby is very ill—nurturing touch may be a viable substitute. In 2012, Inder's team conducted a pilot study of what is known as the M technique on infants born nearly three months early to observe their responses to just five or ten minutes of this technique's gentle, stroking massage. Overall, the babies responded in ways that indicated this simple intervention had benefits: the babies' heart and respiratory rates decreased.

"They need intensive care," says Inder, "but they need their brains—and their bodies—to be nurtured."

The sense of touch is structured much like other sensory systems. The retina of the eye, for example, contains specialized cells that detect light, process it, and then send those electrical messages to the brain for further interpretation. Similarly, the skin is packed with sensory neurons that detect touch and then send the sensory information to the spinal cord and brain stem for further processing and interpretation.

To many researchers, it seems clear that just as young brains need to gather and process visual information in order to allow the visual system to develop properly, the developing brains of infants need to experience touch to allow proper development of the somatosensory system, which governs the sense of touch.

"The idea that nurturing touch is essential for normal brain development seems obvious," says David Ginty, the HMS Edward R. and Anne G. Lefler Professor of Neurobiology. Ginty studies the somatosensory system, which is the body's system for gathering sensory information from the skin and processing it for behavioral and survival purposes.

For more than 20 years, Ginty investigated the development of the somatosensory system, learning about the different types of touch-sensing neurons and how they project to, or innervate, the skin.

There are, he says, seven or more types of touch neurons that send their processes into the skin and are sensitive to gentle touch. Each has its own specialty. Some respond when hairs protruding from the skin are deflected, others to indentation of the skin, others to stroking. They also send signals at different rates, some fast, some slow, some continuous. Some respond instantaneously, then go silent.

"It's a remarkable combination of specialized but overlapping sensitivities from different types of tactile stimulation," he says.

About ten years ago, however, he hit a wall. Not enough was understood about the structure and function of the touch sensing system to effectively study its formation.

"Development is a more compelling question when you understand what a system is developing into," he says.

Fortunately, during the past decade, the tools of genetics have allowed Ginty and colleagues to probe the somatosensory system as never before. They have begun using genetic approaches to visualize the skin endings of the seven touch neurons by silencing different genes and precisely stimulating specific nerve cells in animal models to tease apart the system's organization and function. These approaches are helping them understand how the brain processes signals into felt sensations and behavioral responses.

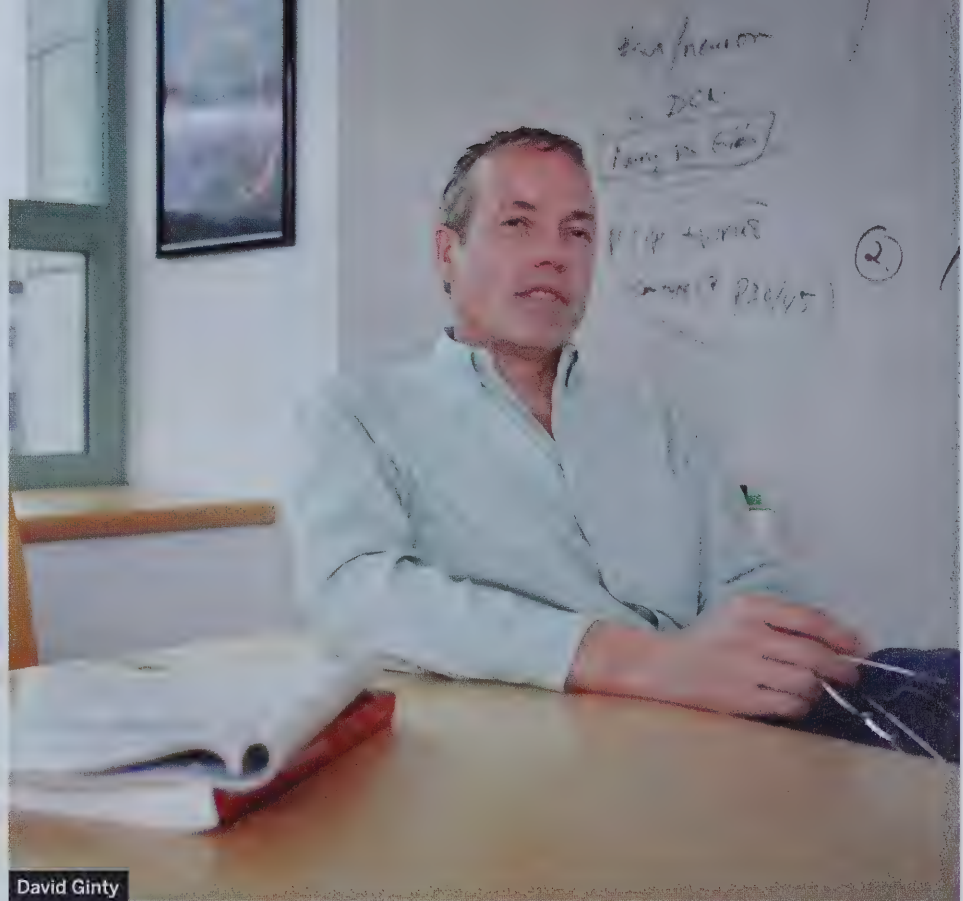
His lab recently uncovered a connection between gentle-touch neurons and anxiety. He and his team studied mice that had been genetically engineered to model autism-spectrum disorders. Each model involved knocking out or mutating a single gene that is associated with the disorder in humans. They found that the gene alterations affected the neurons activated by gentle touch by effectively removing volume control.

"The animals experienced a touch signal-ing overload," says Ginty.

The mice also developed anxiety that persisted into adulthood. The anxiety developed, however, only if the gene mutation was introduced early, before the mouse had grown into an adult. If the mouse lost the gene as an adult, the animal experienced the hypersensitivity to gentle touch but did not develop anxiety. The finding suggests not only that there is a critical window during which touch sculpts the nervous system, but also, says Ginty, that "normal developmental touch may be required for prevention of this form of anxiety."

The study opens a door for Ginty to begin to understand how touch influences brain development. He now has a model system in which he can reliably perturb the signals coming into the somatosensory system and explore the effects on long-term well-being.

"The opportunities in this field are incredible right now," says Ginty. "I think over the next decade we'll begin to understand the mechanisms behind the holistic response to light-touch processing, including the importance of nurturing touch for brain development."



David Ginty

Can't Touch This

Worldwide adoption of kangaroo mother care remains very low, at an estimated 5 percent, says Chan, who recently launched a study aimed at analyzing and refining programs intended to encourage kangaroo care adoption and use in hospitals in Ethiopia and India.

There are many reasons, however, why kangaroo care has not been more widely adopted in neonatal intensive care units. One is space. These types of care units are notoriously cramped places with little room for snuggling.

Even when space is available, nurses, doctors, and parents must learn how to move the fragile babies in and out of the incubators without disturbing critical tubes and monitors.

"I didn't realize how challenging it would be to implement an intervention like kangaroo mother care," says Chan. "Some ideas are adopted quickly, but the slower ones are usually those that require a lot of behavioral change, and those in which the benefits are not seen right away."

Margaret McConnell, an assistant professor of global health economics at the Harvard Chan School, offers yet another barrier to implementing this type of care.

"There's this sense that it's very cost effective, but no one considers the cost to moms," she says.

It can be difficult for families to find the time and money to support daily hospital visits, especially if time off from work is

limited, if there are other children to care for, or if the neonatal care unit is far away.

"Even for affluent mothers, the costs can be significant," says McConnell. To better assess whether certain interventions could help mothers whose babies might benefit from being involved in a kangaroo care program, McConnell and colleagues at the Harvard Chan School are collaborating with clinicians at Tufts University Medical Center on an initiative that provides cash support to mothers. Their aim is to see whether this intervention affects the time mothers are able to spend providing kangaroo care for their babies.

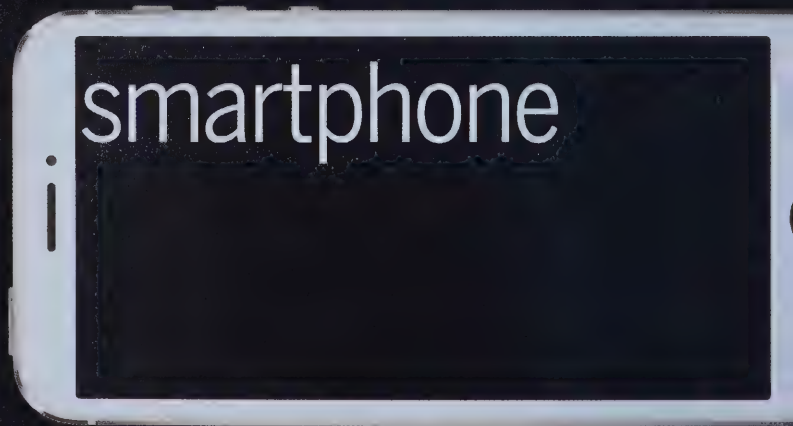
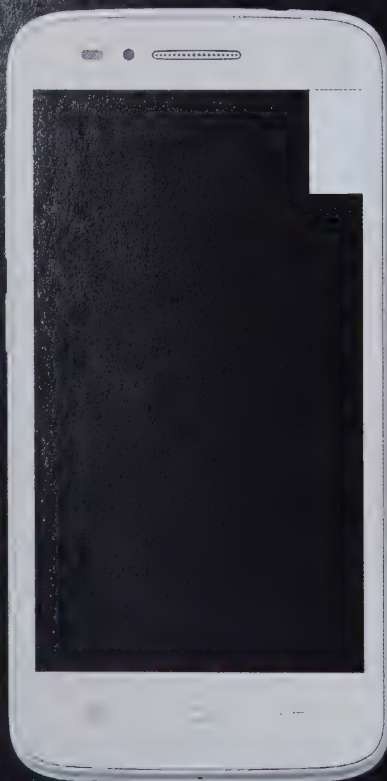
McConnell's work raises a direct question: Is nurturing touch medicine? The clinical evidence suggests yes, as does the evidence being uncovered by neurobiologists who study touch.

Yet the idea is a sharp turn for some neonatologists, for whom the cost of investment may be measured in credibility.

"Neonatologists are trained as intensivists," says Inder. "We like numbers and control. When we started to think about kangaroo care, some colleagues thought it made sense. Others said, 'What happened to you? You used to be such a good neuroscientist. Now you've gone all fluffy.'"

But, she adds, "This is where the data are taking us." ■

Elizabeth Dougherty is a Massachusetts-based science writer.





Does digital communication affect our sense of belonging?
by Stephanie Dutchen

Place the winky face emoticon where you think it best fits: Social media makes you feel lonely. Social media makes you feel less alone. Smartphone use damages relationships and facilitates ideological echo chambers. Smartphone use strengthens bonds with others and exposes us to more diverse opinions. ■ According to the Pew Research Center, three-quarters of U.S. adults own smartphones and three-quarters of teens own or have access to one. Ninety-two percent of teens go online daily, 24 percent of them “almost constantly.” Ninety percent of teens and 65 percent of adults use social media. >>



Michael Rich

AS

online life grows and headlines speculate about whether social media will be the downfall or the savior of human civilization, researchers struggle to understand how digitally mediating our interactions deepens or damages our sense of belonging, which in turn could influence the health of individuals, relationships, and communities.

"Digital media is arguably the most universal environmental health issue in the twenty-first century—as important as immunizations, bicycle helmets, and safety belts," says Michael Rich '91, an HMS associate professor of pediatrics at Boston Children's Hospital and an associate professor at the Harvard T.H. Chan School of Public Health.

Pinpointing the effects of digital communication on social structure and function, however, is proving extremely difficult.

Investigations by researchers throughout Harvard University into the effects of social media on human happiness and healthy aging, child and adolescent development, interpersonal communication, and engagement in civic society are finding cause for both optimism and concern.

What's on Your Mind?

Because it's increasingly clear that every person who uses the internet uses it differently, researchers are working to discern who might be helped and who might be harmed by socializing online. Young people, many of whom are digital natives, tend to develop different habits from older adults, the digital immigrants. The rate of change is so rapid that Rich reports seeing norms shift not only between generations but between siblings. Even within the same age group, people's preferences for engaging with others—text? tweet? in person?—varies, as does their comfort with using smartphones in social settings and their susceptibility to feeling isolated or welcomed in online spaces.

"One size doesn't fit all," says Robert Waldinger '78, a psychiatrist at Massachusetts General Hospital and director of the Harvard Study of Adult Development at the hospital, who helps his patients examine how they feel when they go online and how internet use affects their lives.

According to Robert Putnam, the Peter and Isabel Malkin Professor of Public Policy at Harvard University and former dean of the Harvard Kennedy School, robust social networks have been shown to be one of the more powerful determinants of individual health and well-being, but it's not yet clear to what extent virtual networks confer the same benefits.

Waldinger would agree. "What worries me is we're being shaped by these new technological advances, and we don't understand how. Often we don't understand change until we look back on it."

Rich and colleagues are attempting to understand how social media's influence might begin to be analyzed. One way they're doing this is by examining where online relationships fall short of "real-life" ones and how those shortcomings might be mitigated.

"We've got the developing human being, and we've got the evolving environment," says Rich. "Part of what we're trying to do is collect an evidence base so that we can come to some fundamental understanding that is not Luddite in nature."



Robert Waldinger

Alison Wood Brooks, an assistant professor of business administration and Hellman Faculty Fellow at Harvard Business School, is seizing the opportunity to exploit digital technologies to understand how they're affecting our interactions and sense of inclusion or ostracism.

"People are plugged in all the time," says Brooks, "which means we can track behavior and cognition precisely and carefully over time. That's exciting."

Tweeting in the Key of Me

In 2000, Putnam published the national bestseller *Bowling Alone: The Collapse and Revival of American Community*, an extensive exploration of the rise and fall of civic engagement in the United States over the course of the twentieth century. Putnam documented how participation in local and national groups, from bowling leagues to political parties, peaked between World War II and the social movements of the 1960s and plummeted in the following decades. He assessed an array of potential contributing factors, fingering generational differences and the introduction of television as the two biggest culprits, and warned that unless trends reversed, community and individual health would crumble too.

Social scientists theorize that a thriving society built on mutual trust and support needs two kinds of social capital: bonding, which strengthens ties among members of a particular group, and bridging, which forges connections across groups. Bridging is harder. It requires people to regularly interact with and get to know people of different races, religions, socioeconomic classes,

sexual orientations, gender identities, and political views.

According to Putnam, the United States has a major bridging-capital deficit. Although efforts to erase racial and religious segregation have modestly improved things in the past 50 years, class and political divides have widened, he says. People tend to live near and associate only with people like themselves.

"I think that's extremely dangerous for our country," says Putnam. "We're all here living together, but we're living in separate societies."

A study published in 2014 in *Psychological Science*, which looked at data through 2012, indicated that social trust had continued the decline Putnam's work had found. Putnam, however, points out that the digital revolution arrived too recently to have caused the deterioration his research identified.

Everyone seems to have an opinion on whether the internet, particularly social media, has widened intergroup gulfs by letting people indulge the human tendency toward tribalism or narrowed those gaps by giving people unprecedented access to a near-limitless variety of the human experience. Individual studies provide support for each argument. While evidence continues to be gathered and weighed, Putnam predicts that social media has tipped the scales too far toward bonding at the expense of bridging.

"The early hype about the internet was, it was going to be completely bridging," says Putnam. "That is, and always was, nuts."

Despite the fact that the internet bridges geographically, it can engender what technophiles call cyberbalkanization or the splinternet: insular online communities of people

who have the same interests or ideologies and who are often of similar social class and education level. What at first seems like a boon for people's sense of belonging can lead to polarization, extremism, and a distrust of outsiders.

"It's fun and fortifying to be around people who agree with you," says Brooks, "but being surrounded by only like-minded people can prevent us from learning from others' differences and from understanding a diversity of perspectives. We need a balance of agreement and disagreement in our lives."

Of Human Bonding

Boosting bonding capital isn't always bad. The internet has allowed people who feel alone because they're a minority in some way—including LGBT youth, people with disabilities or illnesses, and people with niche passions—to find others like them and to build secure, supportive relationships.

"For isolated people with a unique situation in their lives, the internet is a blessing," says Waldinger.

A 2013 report from the Gay, Lesbian and Straight Education Network (GLSEN), based on surveys of nearly 5,700 U.S. students in grades 6 through 12, provided early documentation of exactly how much online relationship building has helped young lesbian, gay, bisexual, and transgender people. In addition to finding information about health and sexuality that wasn't available to them offline, LGBT youth were more than twice as likely to have at least one close friend online and rated their online friends as more supportive than non-LGBT youth did. And although young LGBT people were more likely than their non-LGBT peers to be bullied or harassed online, social networks offered them "critical tools for coping with these negative experiences," said Michele Ybarra, research director of the Center for Innovative Public Health Research, in a GLSEN press release. The center helped conduct the study.

Throughout the past two decades, similar success stories have emerged involving online connections among patients, loved ones, and caregivers. Online exchanges allow people to share details about rare conditions, provide emotional support, and, occasionally, gather enough momentum to secure funding that directly supports research and even helps shape federal policies.

Recognizing the potential of the internet to help his patients, Rich is establishing limited-access social media platforms where



Robert Putnam

kids and teens with chronic medical conditions can connect with one another about their experiences and share videos they've created about their illness experiences. The idea stemmed from a project that began in the 1990s, when Rich handed video cameras to his patients with asthma.

"I wanted them to teach their doctors what it was like to live with their illness," says Rich.

Now, of course, his patients record everything with their smartphones. In their social media environments, they build community out of isolation, crowdsource life strategies, and receive care from and offer care to their peers.

"The coolest thing we found is that, just from the self-expression, these kids got better in disease-specific, measurable ways," Rich says, including improved quality of life and self-management skills.

Hearing their experiences echoed by online acquaintances can be a major boost to mental health and self-esteem at a stage of life when many teens feel pressure to fit in and be "normal." Listening to the stories and paying attention to the day-to-day environments captured in these videos has also helped Rich and other doctors better connect with their patients, which can lead to well-tailored treatment plans and greater adherence to those plans.

Interacting with others through screen and keyboard can be a boon for people on the autism spectrum or those with social anxiety who want to build stronger relationships, helping them develop deeper connections

than are possible or comfortable in person. For some, the confidence and interpersonal skills honed online carry over into offline life.

The wired life also provides opportunities to build trust between doctors and young patients.

"Look at what devices the kids bring with them into the clinic. Ask what they're watching and listening to. It gives you information and it shows your respect for their world," says Rich. "Then you can have a more open conversation."

Screen Grab

A 2016 study in the *Proceedings of the National Academy of Sciences* of 12 million Facebook users in California and comparable non-users found that social media engagement—especially aspects that indicate offline social connections, such as posting photos—correlates with reduced mortality, including fewer instances of heart disease, dementia, and diabetes. The links were strongest when users accepted friend requests from others.

According to Waldinger, data collected from participants in the Harvard Study of Adult Development have shown that high-quality, close relationships are the best predictor for aging well. The study has followed two socioeconomically disparate cohorts of Boston-area men for more than seven decades and is now being extended to follow their children.

Waldinger and others agree that one of the strengths of social media is the opportunity it provides to sustain relationships between

in-person encounters with friends and family. Even so, they underscore some irreplaceable benefits of face-to-face interaction.

"Most of our networks nowadays are alloys that combine virtual and 'real' connections," Putnam says, "and we don't yet know the long-run effects of different types of alloys."

Rich, for one, thinks that part of the allure of email, texting, and social media is that it buffers people from the scarier aspects of face-to-face communication, especially issues of "hot" emotion, like attraction. But tweeting and texting, he says, even about deeply personal topics, can't replace the trust and intimacy of confessions whispered in the wee hours of an old-fashioned sleepover.

In Emoticons We Trust

Like Rich, Brooks has documented ways in which online communication feels easier but may not benefit relationships in the long run. She studies the psychology of conversation and emotion, including some of the strengths and pitfalls of online interaction and what we can do to overcome its deficiencies.

"Face-to-face communication is difficult and depleting. You have to simultaneously pay attention to what the other person is saying, monitor his facial expressions and body language, try to perceive his emotional expressions, all while monitoring yourself and what you're trying to say and convey back," she says.

Brooks proposes, however, that the asynchronous nature of email and platforms like Facebook allow people to take time to consider their replies and wait for intense emotions to abate. That could be a good thing, or it could prevent honest communication.

The flip side of text-based conversations is that they "can be impoverished. You miss facial expressions, body language, emotional perceptions—face-to-face cues provide a great deal of information that helps us make important social judgments," she says.

One way to compensate for some of the shortcomings of digital communication is to use emoticons. Brooks's ongoing research has shown that using more, and more diverse, emoticons when talking to others online appears to bestow greater happiness in people's lives and relationships.

Another way to forge a sense of trust or belonging online is to increase empathy by asking other people questions, Brooks says. "There's an overwhelming majority of things said online that end in periods rather than question marks. Empathy often ends in question marks. It doesn't state; it asks."



Allison Wood Brooks

Brooks adds, “Think of LinkedIn, Facebook, Instagram. People are much more likely to publicly reveal their successes than their failures. This tendency contributes to an online culture of anxiety where everyone feels like a failure compared to their peers.” She and Karen Huang, one of her doctoral students, have done research that Brooks says shows that “if successful individuals reveal their struggles and failures in addition to their successes, they are likely to strip away resentment. Onlookers feel less of the malicious envy that makes them feel bad about themselves and makes them want to tear down others who are successful. Instead, they feel more benign envy—a sense of belonging, community, and motivation to improve their own station.”

“Don’t hide your flaws online,” agrees Rich. “Be vulnerable. The relationships that matter happen in spite of, or because of, those flaws.”

Retro Appeal

Complaints about the detrimental effects of communications technology on human relationships and society are surely as old as technology itself. Plato lamented that adopting written language would invite misinterpretation, prevent discussion, and destroy

People are plugged in all the time, which means we can track behavior and cognition precisely and carefully over time. That’s exciting.

people’s memory capacity. When the printing press was invented, Benedictine monks warned that it would spread misinformation, degrade the art of letters, and corrupt and inflame “impressionable youths.”

Yet, history informs. After a hue and cry about how the telephone would turn everyone into social shut-ins, studies suggest it reduced face-to-face interaction but also reduced loneliness. A few decades later, televisions infiltrated U.S. homes, and social capital took a nosedive. Researchers determined that higher screen time lowered social engagement.

As both a communications vehicle and an opportunity to spend hours passively staring at a screen, the internet can’t be mapped directly onto either of those technologies.

“Most online time replaces TV time,” says Putnam. “On the other hand, there’s some evidence that some internet time comes from ‘real’ social activities.”

The past teaches another lesson: that it’s not easy to foretell the social repercussions of disruptive technologies. “For those of us who wish to anticipate the impact of the Internet on social relations, the astounding series of poor predictions about the social consequences of the telephone is a deeply cautionary tale,” Putnam wrote in *Bowling Alone*.

As the story continues to unfold, Rich celebrates social media as “an immense opportunity for self-expression,” while Waldinger approves of the doors the internet opens for self-affirmation. “There’s more ability to understand who you are in relation to other people,” he says. “There are more ways of understanding yourself. It can feel less isolating and weird. I think that’s all really hopeful.” ■

Stephanie Dutchen is a science writer in the HMS Office of Communications and External Relations.



(un) intended conse- quences

Unconscious bias hurts individuals on both sides of the white coat
by Jake Miller

Does pain have a color? If, in 1993, you were reading a certain study in JAMA, you might think it did. Or you might think pain manifested differently according to complexion. Why? Well, that JAMA article reported that Latinos with a broken arm or leg were two times less likely to get pain medicine in a Los Angeles emergency department than whites with similar injuries.

FARM SECURITY ADMINISTRATION OFFICE OF WAR INFORMATION (FSA-OWI) / LEE / 21 C. E. B. / 21 C. E. B.



Titled "Negroes in front of doctor's office in Merigold, Mississippi," this photo was taken in late 1939 by Marion Post Wolcott, a noted U.S. photographer who worked for the Farm Security Administration during the Depression. Wolcott was a social progressive who sought to capture images of situations that needed redress.



But felt pain was really not the issue. The issue was how relief was meted out.

That study was an early ripple in a wave of findings showing an inequity in the delivery of health care. By 1999, Congress was asking the Institutes of Medicine—now the National Academy of Medicine—to investigate the situation. In their 2003 report, *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care*, the authors noted that “racial and ethnic disparities in healthcare ... are consistent and extensive across a range of medical conditions and healthcare services, are associated with worse health outcomes, and occur independently of insurance status, income, and education.”

The report’s authors also wrote that while “myriad sources contribute to these disparities, some evidence suggests that bias, prejudice, and stereotyping on the part of healthcare providers may contribute to differences in care.”

A growing body of research has shown that implicit bias, also referred to as unconscious or unthinking bias, is widespread and affects, for example, women, people of color, and those who have disabilities or who are overweight.

Recent studies have found that discriminatory actions based on such biases contribute to poorer health care. In addition, there’s evidence that experiencing short- or long-term discrimination can increase the risk of many diseases throughout a lifetime. Research on medical education itself has shown that unconscious bias can impede academic performance among minorities underrepresented in medicine. It also can impede progress toward diversity in medicine, a goal that leaders in academic medicine say is crucial to ensuring the delivery of quality care to all people.

Test Roles

For a good number of years, researchers have been trying to get a handle on implicit bias: why it develops, how it is expressed, what its outcomes are. Two people who are active in this area of investigation are experimental psychologists Mahzarin Banaji, the Richard Clarke Cabot Professor of Social Ethics in the Department of Psychology at Harvard University, and Anthony Greenwald of the University of Washington Department of Psychology. They developed the implicit association test (IAT), one of the most widely used tests for the measurement of such bias.

In the 2013 book *Blindspot*, Banaji and Greenwald describe how they developed the IAT. Humans find it easier to sort things into categories that are cognitively connected.



Mahzarin Banaji

People can, for instance, separate red playing cards from black more quickly and with fewer mistakes than they can sort clubs from hearts and diamonds from spades. Building upon this observation, in 1994, Greenwald developed a computer program that presented faces, both Black and white, and words in rapid succession. He then determined the cognitive connections that were made in those who participated.

It turns out that faces of Blacks were more quickly matched with negative words. White faces, by contrast, were more quickly associated with positive words. This biased association persists. In the years since the test was developed, nearly 75 percent of those who have taken the Black-White IAT found it easier to match white faces with favorable words. This response, write Banaji and Greenwald, can best be described as an “automatic White preference.”

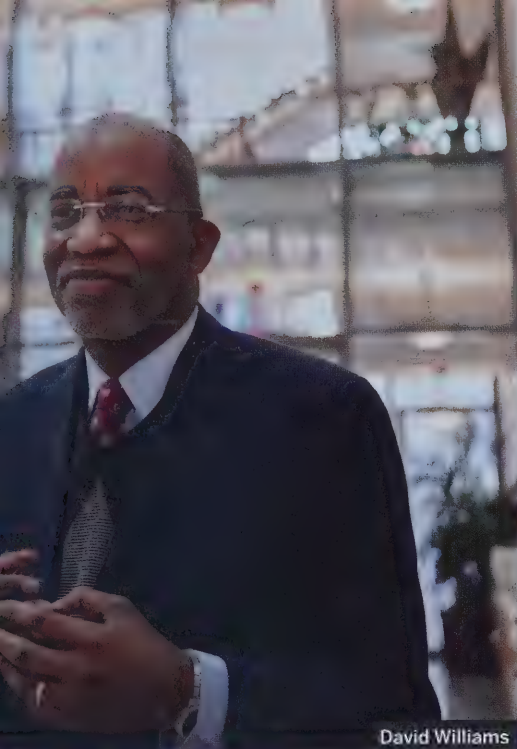
Would these results hold if the test population were made up of physicians? To a large extent, yes, according to a 2009 study in the *Journal of Health Care for the Poor and Underserved*. For this study, a diverse group of more than 2,500 physicians voluntarily took the Black-White IAT online over a two-year period. When analyzed, the investigators found that white, Asian, and Latino doctors showed a preference for whites. Black physi-

cians, however, exhibited no significant racial preference.

To determine whether such preferences played out in the clinic, Banaji and colleagues tested whether scores on the test predicted any differences in diagnosis, referrals for care, or other measurable characteristics of clinical encounters.

In their 2007 paper on this question, reported in the *Journal of General Internal Medicine*, Banaji and colleagues showed a group of physicians vignettes of Black and white patients who were presenting with symptoms of an acute coronary syndrome marked by impaired blood flow, which can lead to organ and tissue damage. They found that physicians who exhibited a high pro-white bias on the IAT were less likely to refer Black patients for thrombolysis, a treatment that helps dissolve blockages in blood vessels, thus improving blood flow and potentially preventing further physiological damage.

In work published in the *American Journal of Public Health* in 2012, Greenwald and others found that primary care physicians who exhibit high unconscious racial biases in the IAT tend to dominate conversations with Black patients, often failing to gather sufficient details of the patients’ social and emotional needs. This dynamic leaves patients feeling unengaged and dissatisfied with the care they



David Williams

receive. Lower engagement and satisfaction can themselves have consequences: Research has shown that patients who feel this way and have illnesses such as diabetes and depression are less likely to follow treatment regimens that would control their conditions.

Proof Sheets

"I like to tell my students that I am a prejudiced person, because I think of myself as a normal human being. These are very human processes that occur in all of us," says David Williams, the Florence Sprague Norman and Laura Smart Norman Professor of Public Health at the Harvard T.H. Chan School of Public Health, professor of African and African American Studies, and professor of sociology at Harvard University.

Williams, who was part of the team that wrote *Unequal Treatment*, is internationally recognized as a leading social scientist who focuses on social influences on health, and, in particular, the ways in which race, racism, socioeconomic status, stress, health behaviors, and religious involvement can affect physical and mental health.

In 1995, Williams developed a tool that has provided arguably the best insight into how daily discriminatory acts create burdens for individuals. Known as the Everyday Discrimination Scale, the test consists of a series of simple statements designed to measure the types of and frequency by which a test taker has experienced discrimination. Sample questions give an idea of how the tool probes the issue: are you treated with less courtesy than other people; do people act as if they think you are not smart; are you called names or insulted.



Herman Taylor

If the person taking the test encounters even one situation with a frequency that could range from daily to at least a few times a year, the test taker is asked what might be the reason for such experience. Test takers are also asked to identify themselves using categories that include race, gender, and sexual orientation.

"These measures," says Williams, "capture the impact of little conflicts and little indignities."

Williams notes that researchers have found that people who report high levels of everyday discrimination have elevated levels of coronary artery calcification, blood pressure, inflammation, and sleep problems; more rapid decline in cognitive function during aging; and premature mortality.

The effects accumulate over a lifetime, Williams notes, so that experiencing success later in life doesn't erase the damage done during years of childhood adversity. As an illustration of Williams' point, a 2012 study by a research team that included Herman Taylor '80, leader of the Jackson Heart Study from 1999 to 2014, found that among participants in that landmark assessment of cardiovascular risk within Black populations those with a high lifetime burden

of perceived discrimination exhibited high levels of hypertension.

Sometimes biased diagnoses are a result of flawed research protocols. According to Taylor, who is also the director of the Cardiovascular Research Institute at Morehouse School of Medicine, one way to fix this is to encourage physician-researchers to consider the members of the communities they serve to be equal partners. The Jackson Heart Study is evidence for his point: its participants are "empowered" participants, not passive subjects.

In addition to revealing crucial details about how factors such as social discrimination, genetics, and other influences contribute to cardiovascular disease in Blacks, Taylor said in a recent presentation that the study is beginning to yield insights about characteristics that contribute to good heart health.

Here, again, bias can make it hard to see the important details.

"It's not all deprivation when you talk about African Americans," says Taylor in an online presentation, citing the importance of social connections, community relationships, and neighborhoods within Black communities.



Unconscious bias is common. I like to encourage people to test themselves. It's a very revealing experience for most people.

Vivian Lee

According to Taylor, these and perhaps other yet-unidentified factors may be reasons behind the fact that many Blacks live long and well, despite facing social inequities that are known to have negative health effects.

"The secret to ending disparities and improving health overall," says Taylor, "may lie in not only understanding and ending the effects of deprivation and challenge but also in discovering and applying the promoters of resilience in the face of adversity." Acknowledging and studying good outcomes among Blacks is often neglected, he adds, though they may be critical for revealing new approaches to improved health despite seemingly intractable social inequities.

Deep Focus

Searching for a neurological link to implicit bias has led researchers to use techniques such as functional magnetic resonance imaging (fMRI) to determine which areas of the brain activate when presented information on people we might consider different

from ourselves and people we might consider similar.

In a 2000 paper in the *Journal of Cognitive Neuroscience*, Banaji and colleagues presented findings addressing this question. Banaji's team measured activity in the amygdala of white participants whose degree of unconscious bias had been measured using the Black-White IAT. The amygdala is the region of the brain that triggers autonomic responses to fear.

The researchers found that if a white person with a high degree of unconscious bias was shown faces of unfamiliar Blacks, activity in the amygdala was heightened. But the amygdala in these participants remained quiet when they were shown the faces of well-known and positively regarded Blacks.

"These data," Banaji and colleagues wrote, "show for the first time that representations of social groups that differ in race evoke differential amygdala activity and that such activation is related to unconscious social evaluation."

When we are aware of the possibility of implicit bias and take the time to think consciously, we can overrule the automatic processes. But in fast-moving, complex situations, the brain handles much of the processing in the blink of an eye, Williams says. A busy white doctor meets a new Black patient, for example. Each has just a few moments to react to the other in what is admittedly a stressful environment. Perhaps unconscious bias on the part of the physician manifests as body language that the patient translates as distrust. This feeling causes the patient to withdraw, a behavior the doctor interprets as a lack of cooperation. Alternatively, the doctor may unconsciously associate negative racial images with the patient and provide poorer quality of care without ever intending to do so.

Perspective

To reset or mitigate unconscious bias in the coming generations of physicians, many medical schools are teaching culturally responsive care. The importance of this movement was underscored when the American Association of Medical College's Liaison Committee on Medical Education made such courses a part of the accrediting standard for cultural competence and health care disparities. The rationale for the requirement stated that medical schools must provide "opportunities for medical students to learn to recognize and appropriately address gender and cultural biases in themselves, in others, and in the health care delivery process."

A 2015 study in the *Journal of General Internal Medicine* suggested that, overall, the medical school experience has a mixed effect on unconscious bias in students: Raising awareness about such bias has been found to slightly reduce bias over the four years of medical school. Other training experiences, however, such as students hearing clinical instructors stereotype patients and experiencing negative interactions with others, appear to increase unconscious bias in some cases.

Research published this year in *Teaching and Learning in Medicine* found that the content of a question bank for Step 1 of the United States Medical Licensing Examination could contribute to the development of implicit bias. The researchers found that race was often used in the questions as a routine demographic variable, but without the social or genetic context necessary to make it a useful clinical descriptor. In addition, whites were overrepresented in the question bank compared to their percentage of the U.S. population. Furthermore, in most

examples with white subjects, race did not play a central part in their clinical case.

In questions about Blacks, the person's race was often described as if it were a key factor in the clinical case. For example, the authors noted, people with sickle cell disease in the question bank were always Black, even though the disease is endemic in parts of Greece and India, while many regions of Africa have low prevalence of the illness.

Falsely promulgating the idea that illnesses such as sickle cell disease, cystic fibrosis, or lactase deficiency are related to a particular race, say the researchers, "risks conveying essentialist, genetically based notions of race and ethnicity to students, which could contribute to bias in clinical practice."

Focal Point

Understanding implicit bias and using that understanding to inform the development of an inclusive environment is fundamental to how Vivian Lee '92, guides the work of her leadership team. Lee encourages members of her team to think about their own biases as part of developing an inclusive environment.

"Unconscious bias is common," reports Lee, CEO of University of Utah Health Care

in Salt Lake City, dean of the University of Utah School of Medicine, and senior vice president, university health sciences at the University of Utah, in an email. "I like to encourage people to test themselves. It's a very revealing experience for most people."

Taking the IAT itself doesn't eradicate bias, Lee adds, but it helps raise awareness so that people and institutions can create processes or take measures to reduce its effect when recruiting new leaders for the school or interviewing prospective medical students.

Why does Lee make this a strategic imperative for her organization? She gives two reasons: the community of patients, students, and trainees that the school and its professionals serve is diverse; and diverse perspectives lead to better problem-solving, especially complex problems like those that challenge many academic health systems.

"I think that while most people initially are drawn to others like themselves," writes Lee, "working in a diverse environment is truly more stimulating and rewarding over the long term. We all learn from each other and that makes for a more fulfilling, productive experience, even if sometimes it feels more challenging."

Wide-Angle Shot

The current generation of students is continually engaged with questions of race and social justice as a result of heightened consciousness, media exposure, and activism, says André Churchwell '79, chief diversity officer at Vanderbilt University School of Medicine.

"It's not just on social media," Churchwell says. "These are real situations that happen in the hospital and that you have to deal with."

Churchwell says that he is leading Vanderbilt to embrace a holistic approach to addressing the challenges of bias and social justice. Integrating race consciousness into every aspect of biomedical research and care delivery is important not because it is so-called politically correct language, but because it's medically and scientifically correct, Churchwell adds.

To illustrate the point, Churchwell describes Andrew Jones, a persona created to demonstrate how the different aspects of race and diversity intersect to influence the health of a patient.

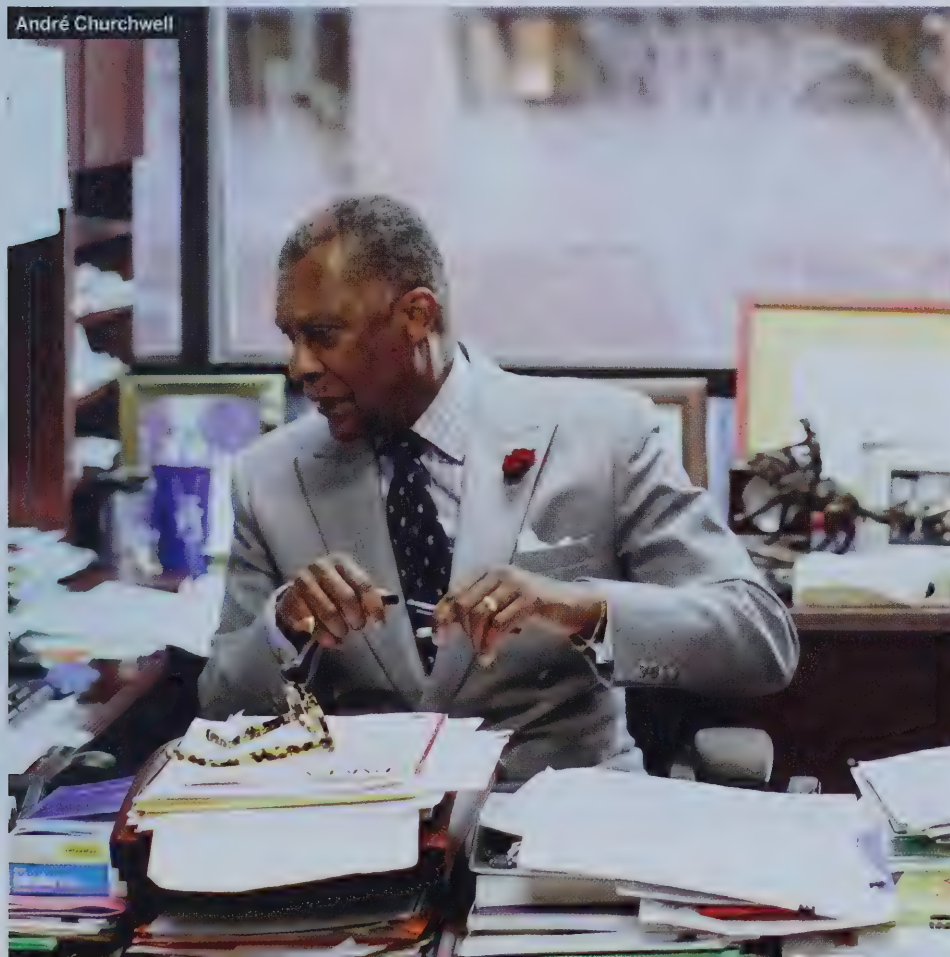
Andrew is a young man with asthma who visits the emergency department often in the summer with acute asthma attacks. A harried ER doctor might assume that Andrew is the kind of kid who doesn't take his medicine on time or follow his doctor's advice and earns return trips to the hospital through irresponsible behavior.

But if you look a little deeper, Churchwell says, you might find that Andrew has a genetic susceptibility seen in the Black community that increases sensitivity to the kind of pollution that worsens in Andrew's neighborhood in the summer, when breezes blow in ozone from nearby refineries.

You need to understand your individual patients in their particular social and environmental context, and you need to understand their illnesses at the genetic and molecular levels, Churchwell says. Then, if you multiply Andrew by 20,000, your understanding expands from a single young man to a community that has its own historical and political context.

"As you try to engage with people, don't think about them as stereotypes," Churchwell says. "As we look at the environmental, cultural and social determinants of health, we must also look inward to combat our own biases." ■

Jake Miller is a science writer in the HMS Office of Communications and External Relations.



André Churchwell



Support System

The bond between doctors knows no borders by Ann Marie Menting

She listened quietly as the physician seated near her spoke. ■ "When the bombs fall, we all mobilize. We know we may die, but we set protocols for what we need to do. We get down to the basement and immediately do triage of the patients who have been injured. ■ "But afterward, we sing, and talk, and laugh. We remind ourselves that we're human, and that we're in this together."

In late July 2015, Michele Heisler met with the speaker, a Syrian doctor, and twenty-three other health care professionals who were attending a conference in southeastern Turkey. She had traveled from Michigan to research the current health situation and the possible targeting of medical personnel and facilities by Syrian government forces in east Aleppo.

The conference that served as the focal point for her efforts was sponsored by the Syrian American Medical Society (SAMS), an organization of U.S. physicians of Syrian descent that has been active in providing aid and support to medical personnel in that country since its civil war began in 2011. The meeting included sessions on the harrowing work physicians lived daily as they cared for residents in east Aleppo, then held by forces opposing the government of Syria's president, Bashar al-Assad.

Some SAMS members, like Chicago-based Samer Attar, traveled several times to Aleppo to spend weeks working beside Syrian doctors, nurses, and other care providers. Other members, such as Pittsburgh-based Ahmad AlhajHusain, set up telemedicine networks to provide counsel and support to those working in hospitals and medical centers in besieged Syrian cities.

A bred-to-the-bone need to deliver humanitarian care drove these physicians to become involved in the Syrian conflict. Yet they were equally compelled by the need to provide community, continuity, and touchpoints of normality to peers who were being pushed to their physical and psychological limits. Like so many physicians who come to the aid of their peers, these doctors are part of the connective tissue that supports and protects those who practice medicine throughout the world.



The writings on the walls of this abandoned hospital in southwestern Syria memorialize fighters and families who died during various conflicts.



All Our Yesterdays

The siege of east Aleppo ended in December 2016, but six years of escalating conflict inflicted scars that deepened daily and will likely remain for generations. According to international monitoring groups, the evidence for crimes against humanity there is unequivocal.

Physicians for Human Rights (PHR), an organization that “uses science and medicine to stop human rights violations,” the group that Heisler represented when she conducted her research in Turkey, monitors and investigates violations of medical neutrality; that is,

the noninterference with medical services in conflict zones. Heisler, a professor of internal medicine and of health behavior and health education at the University of Michigan, began working with the group in the early 1990s when she was a student at HMS. She is now a member of its board of directors. The organization, a co-recipient of the 1997 Nobel Peace Prize, was founded in Boston in the late 1980s by, among others, Carola Eisenberg, then HMS dean of student affairs, and Robert Lawrence ‘64, who was then the chief of medicine at Cambridge Hospital.

As a result of its watchdog efforts in Syria, PHR documented 400 attacks on 276 medical facilities between March 2011 and July 2016. These attacks took the lives of 768 medical personnel. The ramifications of those losses on doctor-patient ratios were vividly portrayed in Aleppo: In 2010, there was one physician for every 800 people; by 2015, that ratio had changed to one for every 7,000 people.

“When we started this work in Syria,” says Heisler, “we assumed hospitals were collateral damage, that they didn’t mean to hit these civilian facilities. But over the years,

The seemingly unending suffering that fills the days and nights of care providers in Syria has taken a steep psychological toll.

Aleppo's original thirty-three hospitals had diminished to ten, which needed to serve a population then estimated at 250,000. Hospitals were not the only item in short supply. In Heisler's report she noted there were only two functioning dialysis clinics, few to no ICU beds in each hospital, and no working CT or MRI machines. Inventories of medicines, syringes, linens, and other supplies were likewise inadequate.

Her report also stated that in 2015 Aleppo had about seventy-seven surviving specialists. This number included one neurologist, one cardiologist, and one thoracic, one renal, and one plastic surgeon; two neuro- and two vascular surgeons; and approximately eight general surgeons.

Although Attar, an assistant professor of orthopaedic surgery at the Feinberg School of Medicine, and other physicians from the United States and elsewhere would periodically augment rosters, Syrian doctors increasingly delivered care that was well outside their specialties. Fortunately, support, guidance, and advice for Syria's care providers could often be found on the other end of an electronic connection.

Tempest in My Mind

About three and a half years ago AlhajHusain, a pulmonologist in the Allegheny Health Network, helped launch a telemedicine effort to support care providers in a small number of hospitals in the Syrian cities of Daraa, Idlib, Aleppo, and Damascus. Starting with four physicians, the network now includes twenty-five doctors in such specialties as radiology, general surgery, neurology, pediatrics, and infectious disease. The Damascus hospital was the first helped by network members. That hospital, like others, was being run by medical students.

"Some of them had never seen a patient," says AlhajHusain. "When we first contacted them, we saw them managing a ventilator machine using settings we never use. It was all wrong, a lot of mistakes."

Over the years, the volunteer network has responded at all hours to texts or calls from medical students, nurses, and even physicians who call seeking guidance.

"We see cases that are very difficult, very hard to manage," says AlhajHusain. "A lot of times, they don't have the medication that's required or the necessary technology. We really have to go back and rely on old medical knowledge to manage cases for which we have no testing."

AlhajHusain's group keeps the communication bridge open using inexpensive cameras, social media applications such as Viper and WhatsApp, and, when available, computers and tablets. Mobile phones, however, are the principal tools for consults—and teaching.

"In the hospitals that are run by students, we hold a teaching round every day," he says. "We discuss cases and give advice. We teach the students because eventually they will need to do this themselves."

Out, Brief Candle

The seemingly unending suffering that fills the days and nights of care providers in Syria has taken a steep psychological toll.

Says AlhajHusain, "Picture this: you're a second-year medical student. You had a plan to graduate and practice medicine, and now that is all gone. Many times, the students go silent, so we have to speak to them, 'Okay guys, what's going on?' They tell us, 'I'm in a besieged area, I have no future, I have no degree. I have no life.'"

"We reassure them that the work they are doing is important," adds AlhajHusain, "that they are heroes to the Syrian people. We have to keep them going. If we disconnect from them, what's that going to do to them?"

Attar has witnessed similar anguish in the physicians he's worked with. "The surgeons," he says, "have told me that they're exhausted. They're sick of seeing children blown up, of seeing all of this death and suffering. But they do their utmost not to show that they're exhausted emotionally and mentally. They feel they have to put on this face of hope for their patients."

"Yet," he adds, "when you see people bleed to death in front of you every day, and there's little you can do except hold their hand, watch them die, and put them in a white shroud for burial, I can tell you that it is emotionally and mentally damaging."

"You can see in their eyes that they're hurting."



The al-Quds hospital in the opposition-held sector of Aleppo was hit by air strikes in April 2016, killing twenty-seven people, including three doctors. Its destruction left only three functioning hospitals in that part of the city.

a number of factors made PHR experts think these were direct attacks."

"For one," she adds, "the hospitals were clearly marked as hospitals, markings that would be visible to bomber pilots. Second is the fact that there were times the military announced it would target a hospital—and did."

Band of Brothers

These overt actions destroyed medical equipment, supplies, and facilities. By late 2015, according to the report *Aleppo Abandoned*, which Heisler co-wrote for PHR, east

To somewhat mitigate these physical and emotional effects, hospitals and medical centers began mandating periodic time outs for physicians, yet many struggled with complying.

One of the physicians Heisler interviewed explained. “I realized I had to take those breaks because I was losing empathy. I was doing surgery and didn’t have anesthesia. But I was not being sensitive to the pain I was causing. I was getting too hardened. I had to replenish myself so that I could be a caring physician.”

According to Heisler, the physical and emotional pressures Syrian physicians and other health professionals have faced for so long could set the stage for an epidemic of post-traumatic stress disorder (PTSD).

“When they’re under siege, they’re able to keep going,” Heisler says, “but after it’s over, that’s when the vigilance, the nightmares, the flashbacks could start.”

Attar, likewise, thinks the trauma of working through years of siege will affect physicians. “They haven’t had time to process it enough. It could consume and overwhelm them.”

Slings and Arrows

Research on the psychological effects that intense, stress-filled trauma care has on health care providers often focuses on first responders, trauma surgeons, and emergency physicians who work in tertiary hospitals and other care delivery settings, usually in regions of conflict. Studies conducted during the past decade, however, have suggested that more than 15 percent of all physicians experience levels of work-related stress that prevent them from discharging their professional responsibilities. Among first responders, the prevalence of PTSD is tenfold greater than that found in the general population and is equal to that seen in military combat veterans. In a 2014 paper reported in the *Journal of Trauma and Acute Care Surgery*, researchers showed that, in a survey of more than 450 trauma surgeons in the United States, PTSD symptoms were present in 40 percent of the respondents. Another 15 percent met the diagnostic criteria for PTSD.

Circumstances contribute. In the 2014 study, PTSD symptoms were most commonly found in male surgeons operating on more than fifteen cases per month, having more than seven on-calls per month, and receiving fewer than four hours of relaxation per day.

A study published in 2016 in the *Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* by researchers at the University of Leiden, reported on results from a question-

naire designed to assess how work-related traumatic events and hectic work conditions affected the incidence of PTSD symptoms and somatic complaints among the nearly 200 Belgian emergency physicians who participated. The researchers found that 14 percent of the participants met the criteria for a clinical level of PTSD. Interestingly, respondents reported that traumatic experiences were highest in situations in which they dealt with the sudden death, traumatic accident, or disease of a young person. Seventy-five percent of those responding had children of their own.

How powerful a psychological blow a personal connection can land was shown in a 2006 study reported in *The Journal of Clinical Psychiatry* by researchers in Israel. The investigators surveyed more than 200 surgical physicians based in two Jerusalem hospitals to determine whether exposure to victims of terror triggered their development of PTSD. They found that the prevalence of PTSD among participants equaled that seen in all hospital physicians: 16 percent. Yet when they looked specifically at the surgical physicians with PTSD, they found that their illnesses were precipitated not by what they saw at work, but by the terror they had been exposed to in their personal lives. A similar link was found

among family practitioners surveyed in 2003 in Bosnia-Herzegovina.

Considering these findings together begins to assemble a picture of what physicians in Aleppo have faced daily for more than five years: long unbroken periods of frequent exposure to trauma cases; the need to care for injured and traumatized children by physicians who may themselves be parents; and terror and trauma in one’s personal life. This confluence of circumstances may well, as Heisler worries, make Aleppo-based physicians a collective index case for an epidemic of PTSD in Syrian physicians.

To Sleep, to Dream

Sorting out the many variables that underlie the development of PTSD has been central to decades of research by Kerry Ressler ’97, an HMS professor of psychiatry and the chief scientific officer at McLean Hospital.

“I think the physician culture is one in which we’re trained to take care of others; trained to be desensitized to death, to the badness of the world; and trained to focus in the presence of stress,” says Ressler. “You get tough by being tough, so historically within the profession, there’s almost an avoidance of the very topic of PTSD.”

Ressler notes that PTSD became formally defined in the 1970s, after the Vietnam War.



Kerry Ressler



Michele Heisler

“You knew you were part of a team, that you were part of this greater sense of purpose. You’re surrounded by all these good men and women who are just there to help people and save lives.”

By 1980, its status as an illness was fixed, meriting inclusion in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders*. In work published in 2016, however, experts in trauma medicine, psychology, and psychiatry in Lublin, Poland, showed that PTSD symptoms have been documented for at least 4,000 years. The long-ago source they cite describes the anguish and sleepless nights triggered in citizens of Ur at the sight of dead bodies that resulted from the nearly twenty-year siege of their city by Sumerians and Elamites, two ancient civilizations that lived in areas of what are now Iraq and Iran, respectively.

“The first thing people should know about PTSD,” Ressler says, “is that it happens after

trauma and is caused by unwanted intrusions of terrifying memories into conscious thoughts, even dreams. The second thing we know is that the more trauma you’ve experienced, the more at risk you are.

“Our research is beginning to explain who is more at risk.”

As reported in 2014 in *The Quarterly*, the newsletter of the Brain & Behavior Research Foundation, Ressler has shown in mice that different versions of genes associated with fear and stress responses are also associated with abnormalities in the amygdala and hippocampus in the human brain, two regions that play a role in our fear response and our ability to learn. The abnormalities are behavioral—an increased reaction to threat stimuli—and functional—a decrease in connectivity between the two regions. Other research, in human identical twins, has shown that 30 to 40 percent of a person’s risk for developing PTSD is genetic. Genetics, says Ressler in a 2016 editorial in *JAMA Psychiatry*, may also help explain why only 5 to 10 percent of those who are exposed to severe trauma develop PTSD.

“We know that individuals with PTSD have epigenetic marks in their genome that are different from those in the genomes of individuals who don’t have PTSD,” says Ressler. “These epigenetic markers might be imprinted early in development as a function of childhood trauma

and then may later put the person at a higher risk for PTSD if, as an adult, they experience a second severe trauma.”

Treatment for PTSD, says Ressler, can follow basic learning theory and exposure therapy. “PTSD is secondary to the trauma learning, so if you are reexposed to the trauma cues, you may learn to no longer be afraid of them.”

Or, he says, it can follow more psychodynamic and existential models that help the patient reconnect with “one’s sense of self in the world, one’s sense of trust in relationships. Being reintegrated with people is core to recovery. Community cohesion and connectedness are critical.”

In Aleppo Once

AlhajHusain, Attar, and Heisler know how important it is to the physicians in Aleppo to maintain connections with others but also with those things that can help them cling to some degree of normality.

“You have to talk with them,” says AlhajHusain. “We talk with them about their personal lives and their problems so that they feel that someone is with them, that somebody feels for them.”

While in Aleppo, Attar learned that despite all the horror, there was a strong sense of community.

“That was one of the positive aspects of working in Aleppo,” he says. “You knew you were part of a team, that you were part of this greater sense of purpose. You’re surrounded by all these good men and women who are just there to help people and save lives.”

During Heisler’s interviews, a number of the physicians had shared pictures they carried of friends and colleagues who had been killed while providing medical care. For Heisler, it was those pictures that spoke more than words of the need for connection and reconnection.

“There was a sense of isolation,” Heisler says, “the wonder of whether anyone in the world cared about what they were going through. It’s as if they were asking, ‘is there really so much indifference to this horror?’ We were so far from being able to imagine all that they had gone through yet we could look at a picture of their friend—who they named—and make that connection.

“By showing me the photo he seemed to say, ‘This is a person, this was my friend. We had lunch together, we were in the operating room together two weeks ago, and now he’s dead. Please care.’” ■

Ann Marie Menting is the editor of *Harvard Medicine* magazine.



It Takes a Village

Scientific inquiry requires perseverance, collaboration, and, sometimes, a bicycle
by Elizabeth Cooney

For weeks, Alex Meeske had been pedaling to Harvard Square and back again across the Charles River, each time carrying a sample of purified protein in his backpack. ■ The HMS graduate student was years into his hunt for an entity those in his field called the missing polymerase. Should he identify the elusive molecular quarry, the discovery might change how researchers approach the search for new antibiotics.



So

Meeske shuttled samples of purified proteins between the Harvard University and HMS labs of Daniel Kahne, the Higgins Professor of Chemistry and Chemical Biology and of Molecular and Cellular Biology at Harvard and HMS professor of biological chemistry and molecular pharmacology, hoping the refined entities would present evidence that an under-the-radar set of proteins was involved in weaving the walls of worrisome rod-shaped bacteria.

For decades, the molecules that created the walls of these bacteria were thought to be a group of proteins called class A penicillin-binding proteins, so named because their presence offered penicillin a target through which it could weaken the protective outer wall of the bacteria. But there were studies that implied there might be a moonlighting enzyme that also built and shaped that cell wall, perhaps in concert with the proteins that bind penicillin.

Meeske kept up his shuttle research for nearly a half decade, working in labs on both sides of the Charles River to mine the expertise of scientists in protein biochemistry, mutation-sequencing techniques, bacterial cell-wall synthesis, and advanced microscopy. The time, patience, and collaboration paid off, however, for this trans-riverine research effort accumulated strong evidence for a possible new target for undoing infectious bacteria such as *Bacillus subtilis* and *Escherichia coli*.

Tech Support

The trail of research that preceded Meeske's began in the 1980s with the publication of a paper, bolstered by another published in the early 2000s, that suggested another polymerase, a linked strand of proteins, was involved in the building of bacterial walls.

Meeske became involved in the research as a result of his work in the lab of David Rudner, an HMS professor of microbiology and immunobiology. Rudner is no stranger to collaboration; today he and Thomas

Bernhardt, an HMS professor of microbiology and immunobiology, co-lead a research "supergroup" that combines their collective knowledge in bacterial microbiology. Rudner, Bernhardt, and former lab member Tsuyoshi Uehara shared with Meeske a deep knowledge of the history of penicillin, the love of exploring the scientific literature, and the belief that they could solve the mystery of whether class A penicillin-binding proteins were acting alone.

In Rudner's lab, Meeske, using technical tools not available to earlier scientists, showed genetically that a protein called RodA helped shape the elongated cylindrical wall of bacteria, even when the usual wall-building suspects were knocked out. But Meeske needed more proof.

He looked to Will Robins, a postdoctoral fellow in the lab of John Mekalanos, the Adele Lehman Professor of Microbiology and Molecular Genetics at HMS, as well as to Eammon Riley, a former research assistant in the Rudner lab, for help in using a method called mutation sequencing. The trio hoped the technique would allow them to find and define the amino acids that were critical to the functioning of the RodA protein on which Meeske had focused. Finding those amino acids would bring them one step closer to knowing the RodA protein was the right target.

It's not surprising that Meeske approached Robins for assistance. According to Bernhardt, Robins is an expert in sequencing technologies. But, Bernhardt adds, he's also an extremely generous colleague, a "connec-

tor" who routinely helps others in the department.

Robins' test results would provide a second verification that Meeske had isolated the RodA protein and nothing else. To help nail down the biochemistry of the protein, Rudner suggested Meeske turn to Andrew Kruse, an HMS assistant professor of biological chemistry and molecular pharmacology, for guidance on purifying the protein of interest.

Pure and Simple

Although the researchers knew RodA played a critical role in cell elongation, they had only indirect evidence that it might be a polymerase: a 1986 paper linking RodA overproduction with more cell wall synthesis in *E. coli*; Meeske's data on RodA's role in helping *B. subtilis* survive without the known cell-wall building proteins; and a bioinformatics connection that Meeske and others had made between RodA and a distantly related family of proteins that acted as polymerases.

What they needed was airtight evidence that RodA could catalyze cell-wall polymerization as they suspected. To get that, they needed to purify the entity and verify that it and only it was the active agent.

"It's really the only way you can definitively show that a protein has a given activity," explains Kruse. "I worked with Alex to develop a purification procedure that allowed him to purify it and still keep it functional."

Sounds simple, right? Well, it's not.





Thomas Bernhardt (left) and David Rudner

Protein purification can be painful, say Bernhardt, Rudner, and other scientists. It is, notes Rudner, where the sweat and tears come in.

Before coming to Harvard, Kruse, whose background is in membrane protein structural biology and biochemistry, had studied a major family of drug targets called G protein-coupled receptors, which pass through cell membranes seven times. Even though RodA was a very different kind of protein, the techniques that Kruse had helped develop while in the Stanford lab of Brian Kobilka, co-recipient of the 2012 Nobel Prize in Chemistry, translated well to the RodA project.

Kruse used antibody affinity chromatography for protein purification. This type of chromatography sets an extremely selective trap for a protein. Once it binds to the antibody, the protein can be washed free of the substrate of contaminants and purified. To ensure they were snaring the protein they wanted, Kruse and Meeske performed some protein engineering tricks that would flag the RodA proteins for capture.

The technique allowed Meeske to perform assays that would confirm that the enzymatic activity he had identified genetically was in fact coming from RodA alone.

"This cross-lab cooperation is representative of the way that many scientific projects work," says Kruse. "The projects require techniques and expertise that are beyond the scope of any one lab. We're still working with David's lab and Tom's lab to build on this research to understand how this protein

Rudner and Bernhardt co-lead a research "supergroup" that combines their collective knowledge in bacterial microbiology.

works, but also, hopefully, to enable the development of a next generation of antibiotics."

Gold Standard

When Ethan Garner, the John L. Loeb Associate Professor of the Natural Sciences at Harvard, first heard of Meeske's work, he knew it would be difficult proving RodA was the gene in question. As a postdoc in Rudner's lab, Garner had made mesmerizing movies of the mystery proteins as they formed hoops around a bacterial cell. Yet he wasn't convinced those hoop makers were equal to the task of building a cell wall.

"I was really skeptical that RodA was the missing transglycosylase, but I hoped for the best," Garner says. "I knew from talking to

Alex at various times that nothing worked, nothing worked, nothing worked.

"Then, as often happens in good science, everything crystallized in two months. Boom! I was ridiculously pleased, pleasantly surprised—amazed."

After the protein had been successfully purified, Meeske carried it across the Charles to Kahne's lab one more time. On the advice of Rudner, Meeske was going to talk with Suzanne Walker, an HMS professor of microbiology and immunology, about his project. Meeting with Walker was important for another reason, Bernhardt had collaborated with Walker and Kahne in the past, using synthetic enzymes they had produced.

Kahne and Walker had created the peptidoglycan building blocks that the cell-wall builders—like RodA and class A penicillin-binding proteins—need to do their jobs. Their synthetic substrate was a highly complex molecular giant that could not be bought off the shelf from chemical suppliers.

Recalls Meeske, "there are probably only two or three labs in the world that would have the peptidoglycan building blocks that Dan's and Suzanne's labs had." And Meeske was about to meet with Walker.

As she learned about the project, Walker pulled out the lab notebooks compiled by a former postdoc in her lab who had recorded some thoughts on how to purify proteins such as RodA.

Walker agreed that they needed to test whether the purified RodA could, when paired with the synthetic building blocks, build a rod-shaped wall. They tried it and a rod-shaped wall appeared. They had proof that the RodA protein was a new class of bacterial cell-wall builder. They also potentially had a novel target for new antibiotics.

Cast Party

Reflecting on the years of work and the collaborations that helped make it happen, Meeske sees the project as the serendipitous result of expertise and timing.

"Membrane protein biochemistry is kind of a niche field," says Meeske. "Having Andrew come to HMS at the moment he did was vital to the project's completion. Having direct access to the mutation sequencing technology that allowed us to do the genetic screen and identify RodA's importance—and to John Mekalanos and Will Robins, who pioneered the technique's development—was another boon. And the collaboration between David and



Andrew Kruse

Tom was, I'd say, elemental to my research and my experience as a grad student."

It was a mix of mentorship and collaboration, for although principal investigators such as Rudner and Bernhardt pursue discoveries, they are also lab leaders dedicated to education, to matching a particular project to a particular student. During the time Meeske was unsuccessfully attempting to purify the protein, for example, Rudner suggested Meeske take a break from the project. Meeske used that break to shake free of the project and instead consider two unrelated avenues of inquiry, each of which produced two papers for his doctoral thesis.

But the case of the missing polymerase called him back, and Kruse's arrival injected new life into the inquiry. Then, together with Garner, they proved that RodA builds the bacterial cell walls for *B. subtilis* and *E. coli* and likely others.

Although Meeske has moved from HMS (he's now a postdoc in the lab of Luciano Marraffini at Rockefeller University), others in the collaboration continue their probe. Garner, for instance, continues to investigate how each of the players—the class A penicillin-binding proteins and the RodA proteins—contributes to growth of the bacterial cell wall and helps shape it into a rod. Currently, it seems RodA acts to form the ribs of the ship while the class A penicillin-binding proteins fill in the rest of the hull.



Ethan Garner

Rudner and Bernhardt appreciate the decades of discoveries that their work rests upon: the 1928 discovery of penicillin by Alexander Fleming; the 1957 work by Jack Strominger, the Higgins Research Professor of Biochemistry in the stem cell and regenerative biology department, and Ted Park to describe penicillin's molecular action; Strominger's later work to identify penicillin-binding proteins; and work by others to show that there were likely other proteins

Institutional support also plays no small hand in the project. Kruse will continue to work with the Rudner-Bernhardt supergroup thanks to a supplement grant from one of the three Centers of Excellence for Translational Research that exist at HMS.

involved in bacterial wall building. They also remain poised for new, incremental advances that are the lifeblood of basic research.

"I think what's nice about the overall team," says Bernhardt, "is how it has brought together a diversity of expertise. We can really attack this problem on many different levels."

"No one planned to bring such a team together," adds Rudner. "It happened because of the combined effect of new hires, shared meetings, and physical proximity." By the latter, Rudner means the common lunchroom where news of equipment gets shared and research ideas get tossed around.

Institutional support also plays no small hand in the project. Kruse will continue to work with the Rudner-Bernhardt supergroup thanks to a supplement grant from one of the three Centers of Excellence for Translational Research that exist at HMS. Funded by the National Institutes of Health, the centers are designed to move discoveries closer to applications in diagnosis, treatment, and prevention of infectious disease. At HMS, the three centers are individually devoted to the study of tuberculosis, virology, and bacteriology.

"I feel more excited about this work these days than ever," says Rudner. "It feels like we can go deeper because of the connections."

Bernhardt agrees.

"I think that's true with most things in science these days. You need a lot of different expertise to really get a full picture of what's going on."

That's how science happens: over decades, over lunch, and sometimes, on a bike ride across a river. ■

Elizabeth Cooney is a Boston-based science writer.

When Paul Dudley White first visited the Albert Schweitzer Hospital in Gabon in 1959, he was struck both by admiration for what Schweitzer had built and by the impression that he'd been transported back in time, "to the Middle Ages to some secluded monastic institution with great devotion to the ideal but not as practically useful in this day and age as certainly it could and should be."

White, a member of the Class of 1911 and one of the preeminent cardiologists of his generation, proposed to Schweitzer an idea he had for conducting research on heart disease in the local population to add to the global knowledge base on cardiovascular disease. Schweitzer reportedly welcomed the opportunity to collaborate on such research and agreed to provide working space and lodging for two researchers working under White's National Heart Institute grant.

The findings of the six-month study, which appeared in the *American Journal of Cardiology* in 1962, indicated that about three-quarters of the participants, both outpatients and inpatients of the Schweitzer Hospital, showed evidence of one or more cardiovascular diseases. Rheumatic heart disease, evidenced by a 6 percent prevalence of mitral stenosis, was the most common, while coronary heart disease was "practically nonexistent."

The authors acknowledged their hope that the study would increase awareness of "our opportunity and obligation to share more generously the life-saving measures of modern medical science with those elsewhere who need so much and have so little."

Although White did not overcome his initial impressions of Schweitzer's approach to practice, his two researchers did come to understand and appreciate Schweitzer's considerable accomplishments. And, although Schweitzer was not an author on the paper, the authors expressed their "deep appreciation" for his "wholehearted cooperation and kind hospitality."

—Susan Karcz



▲ This 1960 Viso-Cardiette, a battery-operated electrocardiograph secured by Paul Dudley White from the Sanborn Company in Waltham, Massachusetts, was used at Albert Schweitzer's hospital in Lambaréné, Gabon, for research on heart disease in the local population.

Opening Remarks

A wide-ranging conversation with the new dean of Harvard Medical School
by Ann Marie Menting

In January, George Q. Daley '91 walked through the door of his new office in Gordon Hall and began his tenure as dean of the Faculty of Medicine, Harvard University. The twenty-second physician to take on this responsibility, Daley joins a line of leaders tracing back to the School's founding family, the Warrens.

A graduate of Harvard University and of HMS, where he followed the Health Sciences and Technology curriculum and also earned a PhD from MIT, Daley did his residency and chief residency in medicine at Massachusetts General Hospital, fellowship training at Brigham and Women's Hospital and at Boston Children's Hospital, then pursued a clinical practice in hematology/oncology at Mass General and at Boston Children's. Since 1995, he has been a member of the HST faculty and, since 2010, a professor of biological chemistry and molecular pharmacology at HMS.

As a leader in stem cell biology and cancer research, Daley helped found the Harvard Stem Cell Institute and has been pivotal to the stem cell transplantation work undertaken at Boston Children's and at other institutions at HMS. His love of research is deep, so deep that he has decided to maintain his laboratory at Boston Children's during his tenure as the School's dean.

Shortly before assuming his new role, Daley talked with *Harvard Medicine*. In a conversation that ranged from student financial aid to the science pipeline, from diversity to Immanuel Kant, and from research-facilities sharing to fishing, Daley displayed a clear-eyed enthusiasm for the role that he envisions for academic and clinical medicine at HMS.

JOHN SOARES





HM: The School's mission is to create and nurture a diverse community of the best people committed to leadership in alleviating human suffering caused by disease. That's a tall order. How do you hope to approach helping the School continue to fulfill that mission?

GQD: I honestly think Harvard Medical School has multiple missions: to excel in fundamental research and discovery, to be an innovator in health care delivery and access to health care, and to continue to evolve how we educate our students to ensure they develop as practitioners who are comfortable with their role at the interface of science and medicine. As I look across these missions, I know I want to make a difference in how HMS addresses all of them.

I think the School has a responsibility to push the frontiers in every field. We're all about excellence, we're all about rigor, we're all about being leaders intellectually. HMS must remain a leader across the spectra of discovery, education, and delivery.

HM: Addressing this multiplicity of missions will require building on a sense of common purpose. How do you plan to promote a collaborative environment among the affiliate hospitals, Quad-based research faculty, the students, and the medical school that make up this multifaceted entity we know as Harvard Medical School?

GQD: If I'm going to promote collaboration and help make connections among the members of our community, I need to know well what is happening throughout the School. Therefore, one of the first things I want to do is commission a review of the science done at HMS, including the basic science and the clinical translation done at the hospitals. I want to know the areas in which our faculty are contributing, not just in fundamental laboratory-based science, but also their work in pushing the frontiers of clinical medicine, discovering new therapeutics, gaining insights in health policy, developing new initiatives in global health, and creating new approaches to regulatory science.

I am a big supporter of collaborative efforts, whether in the lab, the clinic, or the classroom. I grew up within the Harvard Stem Cell Institute. HSCI is a vibrant place because investigators from many different institutions share a common purpose, a scientific mission

Medicine is by its nature an unselfish and altruistic calling. The fact that our students bring their idealism with them is part of our great strength.

to advance our understanding of stem cell biology. When HSCI was founded, we also faced an external threat of regulation and funding restrictions, and that, too, inspired us to succeed in our common purpose.

I think science today faces many of these same threats and concerns. So as dean, I plan to start stimulating more opportunities for our faculty to come together around common purposes; common missions; and common intellectual, medical, and social goals. I think we already have common missions around scientific goals, goals that cut across our institutions. If the medical school can provide small amounts of seed funding, convene think tanks and programs that bring together communities so that people can discover the synergies that could exist, we will generate a level of productivity across HMS that will be significantly greater than what our faculty is already doing individually.

HM: That would be a remarkable achievement, given the School is so decentralized. Yet, you have affiliations with the hospitals, the medical school, and with the HMS research community. Do you hope your broad sense of belonging will strengthen your position as someone who can help achieve a greater degree of harmony?

GQD: It is my aspiration. I know it won't work for everyone, but there are certain areas where there are shared interests, where we can come together—for example, sharing core technologies that might be too expensive for an individual entity to maintain. Our recent work to advance cryo-electron microscopy led to the development of a consortium that includes certain Quad departments and hospitals. Cell-processing and cell-manufacturing technologies that help deliver engineered cell products represent another area in which shared resources could benefit our researchers. Cell processing is very expensive and labor

intensive: A centralized core facility shared across multiple institutions could potentially improve our work in these technologies. Chemical screening and the maturation and refinement of chemical matter are other areas where centralized facilities that recognize and exploit economies of scale would make sense. We can do all this at HMS.

We already have a fantastic screening facility and a program in therapeutic science, and we are exploring the idea of an institution for protein innovation. There are advantages to organizing more critical mass around therapeutics development. That's one of the initiatives I plan to amplify.

HM: And in education?

GQD: I'm starting as dean shortly after the launch of our major curriculum revision. I'm excited to help shape its vision going forward. I think it's important to make medical education even more formative, to firmly establish principles of lifelong learning that bring together the strengths of science and the strengths of practice. I also think that it's good that our students get to spend more concentrated time in the hospitals, that they develop a sense of ownership and responsibility for their patients in a longitudinal experience, and that they learn to understand that patient care is a shared responsibility.

I think as we get deeper insights into disease mechanisms, as we fragment diseases into ever more refined genetic subtypes, the ability to understand the way those genes and pathways work will be essential to making accurate diagnoses and prescribing appropriate courses of treatment. I think all this requires a new form of learning, one that makes students comfortable with the interface of science and medicine.

There's also the delivery aspect of health care that not only needs to become more cost-effective and efficient but also needs to address inequities in access and distribution, whether within our local population or across populations globally.

HM: There is growing activism among students on such issues as improving access to medical care and bringing greater diversity into the medical profession.

GQD: And there should be, absolutely. Part of what I'm most proud of and cel-

celebrate among the medical students is that they are engaged. They come to medical school because they want to make a difference, they want to change the world. Medicine is by its nature an unselfish and altruistic calling. The fact that our students bring their idealism with them is part of our great strength. Not only am I inspired by them, I'm expecting them to be activists, to hold me to challenging and high standards—and to hold HMS to those standards. These students are going to lead the world.

HM: Should fostering students' passion for the profession and the people they serve be more deeply integrated into education at HMS?

GQD: Yes. You know, three or so decades ago, I was in medical school with a guy named Paul Farmer. He spoke his mind; you knew this guy had passion. He was already seeing the world as a very small health care community that he would serve. He has inspired generations. I think we've got the next Paul Farmers in our classes right now, just waiting to emerge and flourish. Fostering those passions is one of the reasons we need more resources to support our students. I don't want the idealistic young student to come here and be passionate about becoming a primary care doctor, then realize they will emerge from school \$200,000 in debt.

HM: Many believe that the cost of education also prevents many students from entering a school such as HMS.

GQD: Yes, and I don't want the best and the brightest students to avoid coming to HMS because of the cost of the education. I think it's imperative that we raise more funds for financial aid and financial support so that we build a student body that is representative of the communities we serve. I don't think we should rest until the composition of women and minorities underrepresented in medicine is comparable to the broader community.

HM: What other plans do you have for advancing diversity and increasing the representation of women and underrepresented populations at HMS?

GQD: I'm going to take a very close look at how we're vetting our medical students,

the way we are searching for and recruiting faculty, retaining faculty, and developing faculty, so that I may better understand where the hurdles are for women, for minorities, and for the disabled who seek to achieve success in this community.

I'm also going to establish a task force on diversity and belonging, similar to what has been established at Harvard University. The University task force is taking a comprehensive look at diversity across all schools. Our task force will focus on the issues in medicine that we need to pay more attention to.

HM: What sorts of issues?

GQD: I think we need to focus on the kinds of challenges that face people who want to enter the field of medicine, to get a sense of why young people, for example, choose fields other than medicine for a career. We also need to assess what motivates our students. We need to get a sense of what keeps our faculty satisfied and engaged in academic medicine. And we need to determine why people are leaving medicine.

HM: I'd like to shift focus here a bit to ask about your time as a student at Harvard and HMS. Did you live in Vanderbilt Hall?

GQD: I did! I had a small room with a bathroom down the hall. The room had a couch that was originally a seat from a horse-drawn carriage; something like the jump seat from a car. My room was also right over the dumpster, so I was awakened each morning by the garbage truck—or throughout the night by ambulances. That experience put me on a hair

trigger for sleeping, which served me well during my residency.

HM: With all the responsibilities you have already, and those you'll be taking on soon, do you have time to read for pleasure?

GQD: I love to read U.S. history, but I also love to read economic history. The most influential book I've read recently was Dan Kahneman's *Thinking, Fast and Slow*. It led me to read a number of books by behavioral economists. They got me thinking in a different way about the scientific method and how it helps protect us from our intrinsic, innate cognitive biases.

In college, I started as a philosophy major and studied Kant. I had a whole tutorial with John Rawls, who was a modern Kantian, on Kant's *Groundwork of the Metaphysics of Morals*. I consider Kant to be perhaps the greatest philosopher of all time in terms of his contributions to ethics, moral philosophy, epistemology, and logic.

HM: If you could, would you like to invite him to dinner?

GQD: Yes. And Bacon and Shakespeare. Einstein and Darwin would be two scientists I'd like to share a meal with, too. But I enjoy real dinners with contemporary scientists, too—members of my lab. We organize a lot of social activities, many involving cooking and enjoying good wine. It's a good way to come together and relax.

HM: Someone mentioned to me that you like to fish. True?

GQD: Oh, I've recently discovered fishing! I got into it because it connected me with my two sons. They've picked it up; one son is a real student of the sport.

I'm unsuccessful, sadly. But there is a Zen about it that takes me away from the ongoing buzz of everyday life. I relax and I get to connect with my boys.

We usually fish the Charles River for bass, but up in Maine, we do offshore fishing for stripers. We spend hours on the shoreline just casting and looking out at the beautiful coastline.

It's just wonderful. ■

Ann Marie Menting is the editor of Harvard Medicine magazine.

We need to focus on the challenges that face people who want to enter the field of medicine. We also need to get a sense of what keeps our faculty satisfied and engaged in academic medicine.

FIVE QUESTIONS

FOR CHERI BLAUWET ON INCLUSION



What does diversity mean to you?

It means making sure disability is part of the equation. Our definition of diversity shouldn't consist of checking off a few boxes—race, ethnicity, gender. That leaves out a lot of other elements of the human condition. Inclusion is broad. In universal design, we think a lot about inclusion, with one obvious application being accessibility of buildings and structures.

Most elements of accessibility actually benefit everyone: elevators, curb cuts, and ramps all make it easier for wheelchair users but also help anyone, for example, people carrying luggage, pushing strollers, or delivering packages. Simply put, access makes our world more livable for everyone. We in the disability community know that everybody is only temporarily able-bodied.

How does the idea of inclusion play out in medical schools and in clinics?

In my acceptance speech for the School's 2016 Harold Amos Faculty Diversity Award, I talked about how people with disabilities are so dramatically under-represented within the profession and about some of the tangible and shocking statistics on the lack of people with disabilities in medicine.

We know that even in the past five years, individuals who define themselves as someone living with a disability make up only about 1 percent of current medical students. And we know that, by and large, people with disabilities hate going to the doctor because they feel judged. This feeling has led to an anti-medicine, anti-health care attitude among the disability community toward the medical profession.

What drew you to medicine?

In high school I realized that I liked the sciences and also liked working with people. I always thought medicine would be a good option, and I never really deviated from that idea.

My disabling injury as a toddler, coupled with

Assistant Professor of Physical Medicine and Rehabilitation, Harvard Medical School and Brigham and Women's Hospital

Gold and bronze medalist, 2004 Paralympic Games

Silver and bronze medalist, 2000 Paralympic Games

Winner, women's wheelchair division, Boston Marathon, 2004, 2005; Los Angeles Marathon, 2003, 2004, 2005, 2008; New York City Marathon, 2002, 2003

my mom's career as a nurse, meant that I had a lot of experience with health care. As a child with a disability you develop an early maturity about the health care system. You learn to be at ease when talking with doctors and nurses and to be your own advocate, even from a young age.

What are you working on now?

I look at the effects that organized adaptive sports programs have on the function and outcomes of people with disabilities. I also do a good deal of work with more competitive and elite athletes; in this area, our research is mostly focused on injury and illness epidemiology and prevention.

What is the one thing you'd like people to understand about being an athlete or a person with a disability?

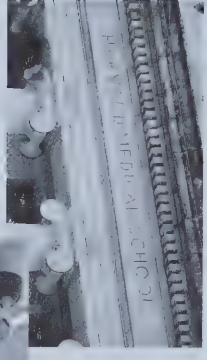
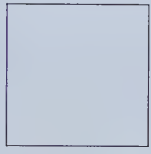
When I was competing a lot, the slogan that I used—and that probably still stands—was, 'no brakes,' which was meant to have a double meaning. As 'no breaks,' people don't want the expectations of them to be lowered. And as 'no brakes,' we want the world to know we are out there to win, to be ultracompetitive, to bring home medals, and to win money, just like any other competitive athlete with high-level aspirations.

We can't expect people with disabilities to do less.

—Susan Karcz



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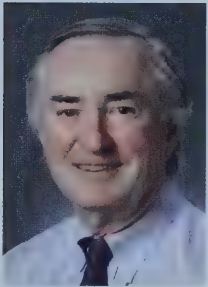
*Graduates from the last nine years are offered a special membership to the prestigious Dean's Council when they give \$100+ for each year since graduation

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THE COMMUNITY OF HARVARD MEDICAL SCHOOL ALUMNI

President's Report



It is an unexpected honor to

serve as president of the Harvard Medical School Alumni Council. I look forward to a year of learning more about our School, and, together with all members of the Council, representing the interests of all HMS alumni.

This has been a year marked by stunning changes, although none more celebrated than the appointment of our new dean, George Q. Daley '91. The Council looks forward to working with Dean Daley to help him achieve his ambitious vision for HMS.

At our Alumni Council meeting in November 2016, I proposed a change in governance to maximize the volunteer efforts of Council officers and to increase opportunities for alumni to serve on the Council and become more involved with the School. Our school needs us now more than ever, and we seek your thoughts and ideas on how to infuse the Council with new projects and ignite enthusiasm among our diverse alumni.

We promise to keep in touch throughout this year of change. Please email me if you are interested in serving the School: hmsalum@hms.harvard.edu.

James O'Connell '82 is an assistant professor of medicine at Massachusetts General Hospital and president of Boston Health Care for the Homeless.



Student Profile | Jessica Ruiz

THOUGHTFUL PLANNING

Caretaking has always been part of the equation

AS THE OLDEST OF THREE CHILDREN in a Mexican-American family in Texas, Jessica Ruiz '18 learned from her elders the importance of setting a good example and being responsible for her younger siblings and cousins.

Ruiz has spent years guiding others and is thankful that throughout her undergraduate and medical school years others have looked out for her. The mentored research she has participated in as an undergraduate and at HMS as well as the support she's received from friends

have helped her find her own way in research and medicine.

As a member of HMS's London Society, Ruiz has participated in the PHACE (Prevention Health Awareness and Choice through Education) program, providing sex education counseling to Boston youth at high risk for teen pregnancy or sexually transmitted diseases. She thinks the program's value lies in making information available allowing teens the chance to ask a physician-in-training ques-

tions about sex—and get candid answers.

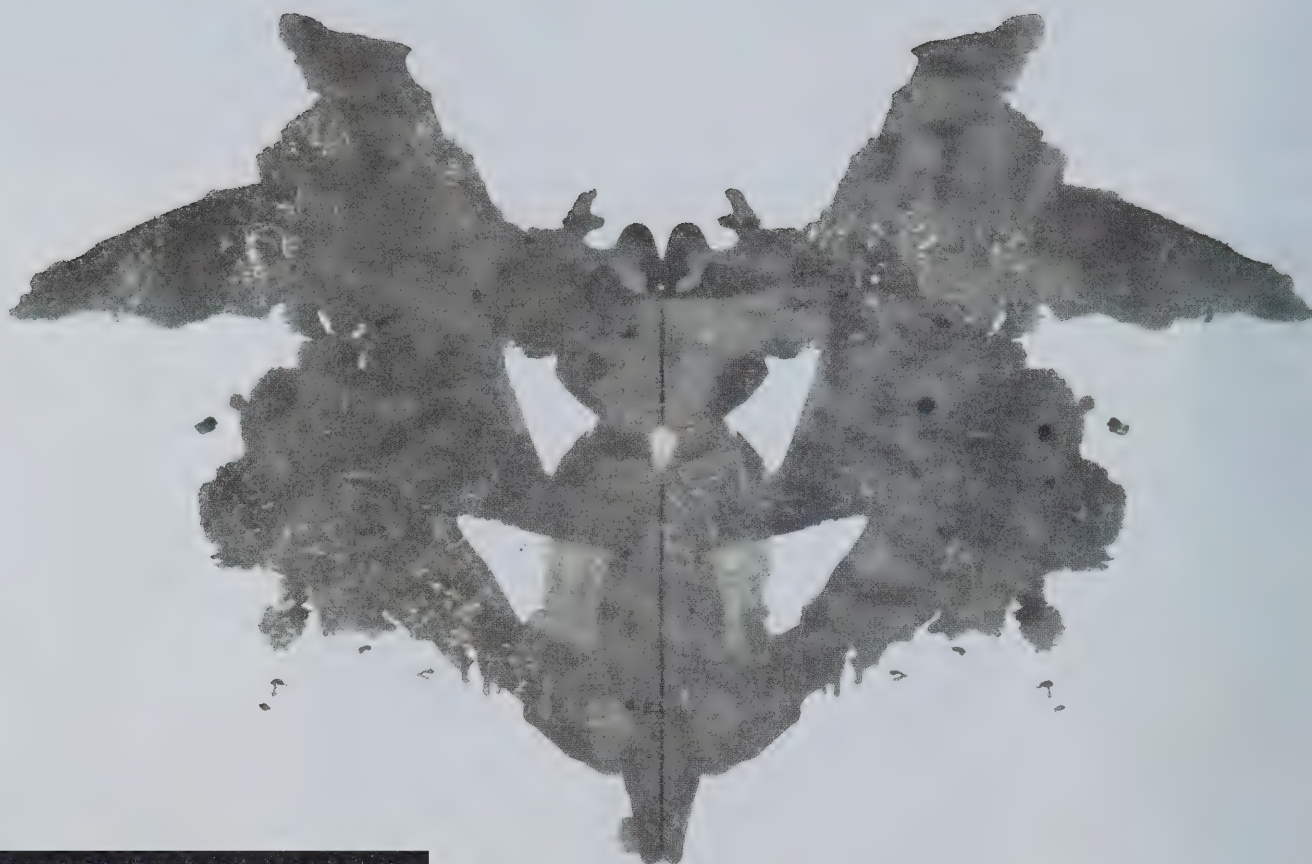
In 2015, as a Howard Hughes Medical Institute Medical Research Fellow, Ruiz conducted research on vascular calcification at Brigham and Women's Hospital. This experience, together with her past involvement in research projects, has Ruiz leaning toward electing pediatric cardiology for her residency.

In order to pursue research work as an undergraduate, Ruiz applied to several programs as a freshman. She was accepted into the National Science Foundation's Research Experiences for Undergraduates program and participated in research that combined biology and materials science.

At HMS, Ruiz has found a niche in the Harvard-MIT Health Sciences and Technology program, where the students form close bonds and help each other through the pressures of med school. She found further support from the network of students she met as an HHMI fellow, with mentoring sessions and other activities that enabled the fellows to share their aspirations and uncertainties with each other.

Besides pediatric cardiology, Ruiz is also interested in pediatric endocrinology and maternal-fetal medicine.

"I haven't found the one, big motivating question that I want to pursue for the rest of my career," Ruiz says, but she thinks the answer may come when she decides what she will do clinically during her third-year Principal Clinical Experience. —Bobbie Collins



The first card of the Rorschach test, developed in the 1920s by Hermann Rorschach. The test is one of several projective tests, which, broadly speaking, are designed to tap the unconscious attitudes or motivations of the person taking the test.

PATTERN RECOGNITION

Older patients fare better with female physicians

YOU MAY LIVE LONGER if your doctor is a woman, according to research published late last year by Ashish Jha '96 and a team of collaborators. And while you're digesting that, think about this: Recent research has shown that significant salary inequities persist between female and male physicians, a discrepancy that previously has been attributed to women's career patterns, with women on the short end of the earnings stick.

Reflecting on the findings, Jha, an HMS professor of medicine at Brigham and Women's Hospital, said in an interview that the salary gap "is particularly unconscionable given the performance of women in terms of providing high-quality care."

Research from as far back as the mid 1990s has reported that women physicians provide higher-quality care and that practice patterns between male and female physicians differ, with women tending to hew to guidelines more strictly, to recommend preventive care more often, and to use patient-centered communication more than their male counterparts.

The recent study by Jha and his team from HMS and Harvard T.H. Chan School of Public Health is one of the first to look into whether

these differences had an effect on patient outcomes. The research also examined whether the influence of physician sex on outcomes differs across disease states and severity of illness. Overall, it provides empirical evidence that patients of women physicians have better outcomes than those treated by men.

The study, published online on December 19, 2016, in *JAMA Internal Medicine*, worked with a sample of Medicare beneficiaries 65 and older who were admitted to acute care hospitals over a three-year period from 2011 through 2014. Outcomes were measured based on mortality and readmission rates within 30 days after discharge.

In a final sample of 1.5 million hospitalizations treated by nearly 58,000 physicians, patients cared for by female physicians had a lower 30-day mortality rate and significantly lower readmission rates after correcting for patient characteristics, including age, sex, race, and primary diagnosis. The authors estimate that 32,000 lives could be saved "if male physicians could achieve the same outcomes as female physicians every year."

Other authors included Daniel Blumenthal '11 and Anupam Jena, of HMS and Massachusetts General Hospital, and Jose F. Figueroa '11, John Orav, and Yusuke Tsugawa, of the Harvard Chan School and Brigham and Women's Hospital.

—Susan Karcz

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THE COMMUNITY OF HARVARD MEDICAL SCHOOL ALUMNI



Student Profile | Benyam Kinde

Spirit of Inquiry

Innate curiosity and an open mind
spur interest in brain research

BENYAM KINDE '18 holds his parents responsible for his interest in science—in a good way. They encouraged Benyam and his older brother, Isaac, who is also a scientist, to ask and answer their own questions.

This spirit of inquiry brought Kinde to HMS, where he led investigations that uncovered a novel role of the MECP2 protein, which is involved in the neurodevelopmental disorder Rett syndrome, in regulating gene expression in the developing brain.

Kinde was already interested in molecular neuroscience when he came to HMS. He knew he wanted to work in the lab of Michael Greenberg, the HMS Nathan Marsh Pusey Professor of Neurobiology, after having heard Greenberg describe the projects that take place in his lab. Starting in the Greenberg lab during his first year of medical school as part of a rotation, Kinde completed a PhD in 2016.

When he was a child, Kinde's father, a California pathologist and large animal veterinarian who had immigrated to the United States from Ethiopia, tutored Kinde and his brother on disease pathology.

Fascinated with watching his father immerse himself in the investigative process—from performing a necropsy to examining tissue slides to developing a hypothesis for why an animal had died—Kinde became excited about applying a methodical approach to understanding the processes that alter normal physiology. His mother, a math instructor at a community college, supported her son's desire to take math and science courses at the college while he was still in high school.

Kinde is passionate about inspiring children to question and engage in science. At HMS, he participated in a program at a Boston-area school where he shared with students the story of his own path from childhood to medical school in the hope of getting the children to think about their own future. In addition, he has traveled to Ethiopia to meet with children there who are interested in science and would like to return to Ethiopia to help up-and-coming scientists.

Kinde's interest in the brain and brain development is pulling him toward clinical training in neurology. "This is an exciting time to be at the interface of basic neuroscience research and the practice of clinical neurology," he says.

—Bobbie Collins

STRESS LESS

HMS launches wellness initiative to help med students learn resilience

FOR SOME STUDENTS, medical school may be the first place they face death, as they begin to confront the reality of their patients' mortality.

The challenges continue as training proceeds. A growing number of studies that have found high rates of burnout, depression, anxiety, and suicide among medical trainees and physicians are causing concern among medical educators.

HMS is launching a wellness and mental health initiative for students that leaders say could help reduce stress and provide medical students with the skills they need to cope with challenges they will face not only during training but throughout their careers.

"The goal is to create a culture of wellness for students and also to give them the skills and tools they can use to manage stress and deal with mental health challenges throughout their lives," says Fidencio Saldaña '01, the HMS dean for students and an assistant professor of medicine at Brigham and Women's Hospital.

The initiative's goal is to assemble a holistic series of programs aimed at promoting wellness and mental health that integrates curricular, extracurricular, and cultural activities

and provides access to advising, mentorship, and mental health resources, Saldaña says.

According to Saldaña, many of these pieces already exist but some need to be enhanced, better integrated, or made more accessible. A recently convened task force of students and faculty members has been working to integrate existing programs with new projects.

The HMS initiative includes a strong component of student leadership, with more than 100 students belonging to a wellness student interest group. This group has launched Sharing Struggles and Building Resilience, a series of talks that highlights coping skills and promotes an inclusive, supportive culture.

The kickoff talk, which touched on impostor syndrome—in which individuals feel they aren't good enough to be where they are in life—and the myth of effortless perfection—the mistaken notion that difficult things are easy for others—was delivered by Edward Hundert '84, dean for medical education and the Daniel D. Federman, M.D. Professor in Residence of Global Health and Social Medicine and Medical Education at HMS.

—Jake Miller

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THE COMMUNITY OF HARVARD MEDICAL SCHOOL ALUMNI



A TOAST TO THE NEW

HMS welcomes Dean George Q. Daley

IN EARLY JANUARY, just days after he had officially begun his term as Dean of Harvard Medical School, George Q. Daley '91 was formally welcomed to his new role by Harvard President Drew Faust and Harvard Provost Alan Garber at a celebration in the Tosteson Medical Education Center.

In a room crowded with faculty, students, and staff, including many from across the Harvard community, Daley noted with gratitude that his mother, wife, two sons, and his five brothers and sisters were all in attendance, along with all of the members of his lab and many close

colleagues from his nearly four decades at Harvard.

In her introductory remarks, Faust said, "George radiates a spirit of optimism, energy, dedication, and ambition that is contagious. We may all join in hoping that this contagion will frequently and rapidly spread."

Daley said he was humbled and honored to be chosen to lead one of the world's foremost medical education and research institutions.

"At Harvard Medical School, each of us is entrusted with making a difference, whether through

biomedical research, education, or patient care," he said. "Each of us is charged with upholding the highest standards of rigor, excellence, and service, no matter what our role."

Daley outlined his thoughts on how the School may best take advantage of the current wave of transformative advances in medicine while confronting the challenges of reduced funding in research, broader cost cutting in health care, and the need for HMS to more fully embrace diversity.

Daley thanked everyone in the community for their dedication to the mission and values of the School, expressing gratitude to Faust and Garber for giving him the opportunity to lead an institution with an unparalleled

potential to deepen understanding of biomedical science and to improve human health.

"I am fiercely committed to our collective mission," Daley said. "For me, this deanship is a call to service."

In a toast to the new dean, Garber said that one essential characteristic that defines Daley is that he is a "both-and" person: at Harvard, he has been both a student and an educator, both a researcher and a clinician. As someone who "doesn't willingly concede that he must choose between two options," Garber said, "Daley is the ideal candidate for this moment of 'significant challenge and extraordinary opportunity.'"

—Jake Miller

CLASS NOTES

NEWS FROM ALUMNI

1945

Giulio D'Angio

Finding what is my third or fourth basal-cell carcinoma, I was reminded of my years as a radiology trainee at the Boston City Hospital in the 1950s. There, without wearing face masks, we fluoroscoped patients with the screens inches away from our noses. The screens, although made of leaded glass, were not impervious to X-radiation. The basal-cell carcinomas and the tuberculosis I contracted from a patient during fluoroscopy are reminders of "how it was back then."

This most recent skin carcinoma, coming more than 60 years after my stint at Boston City, is really a delayed complication of a cancer treatment modality. And I am the one who, in the 1970s, started the systemic study of the iatrogenic late effects of cancer therapies! My hobbyhorse keeps coming back to bite me. Any classmates coming through Philly are welcome to stay on Rittenhouse Square with Audrey and me.

1952 65th
REUNION

Mortimer Lorber

For the past year and a half my wife, Eileen, and I have been living in a tall retirement building in a suburb adjacent to the northwest quadrant of Washington, DC. Many interesting residents, including some alumni of Harvard College and of Harvard Law School and the parents of an HMS alumna, add to our contentment. I maintain a connection to the Georgetown University School of Medicine, although I no longer teach dentistry or physiology to

the first-year medical students, I still dabble in trying to uncover new knowledge. I send best wishes to my classmates and look forward to seeing you in June.

1957 60th
REUNION

Wilbert Aronow

I co-authored *Translational Research in Coronary Artery Disease: Pathophysiology to Treatment*, published by Academic Press, an imprint of Elsevier, in November 2015.

John Parker

I recently developed wet macular degeneration in my right eye and have been treated at University of California Davis Medical Center with an antivascular endothelial growth factor developed by the late Judah Folkman. The results are quite good to date.

Howard Rubenstein

My musical, *Romance of the Western Chamber*, will have its U.S. premiere off-off Broadway in September. The musical, co-written with Max Lee, had its world premiere in Hangzhou, China, in September 2011. It is based on Xi Xiang Ji, a Chinese comedy of the thirteenth century, and a remarkably modern play. If you are in New York in September and have trouble getting tickets to *Hamilton*!, consider seeing the show.

1967 50th
REUNION

Temidowooluwa Ogunye

I am 76 years old and still bubbling with energy, Nigerian style. After the Vanderbilt Hall extravaganza in 1967, I hurried back to



participate in the Nigerian civil war, which was just starting. I entered as a captain and "graduated" in 1970 as a lieutenant colonel. I learned that in the Nigerian Army, a civilian is not just a civilian but a "bloody civilian." I returned to the United States and became board certified in pediatrics, eventually becoming an instructor, and later an assistant professor of pediatrics and genetics at the Howard

University College of Medicine in Washington, DC. Home is home.

1958

George Spaeth

When Ann became very ill in 2013, I stopped all my medical activities, including surgery and seeing patients. After her death I resumed doing research and

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teaching internationally but did not resume seeing patients. I was pleased by the results of a survey by the British journal *The Ophthalmologist*, asking their international readership to rank the top 100 influential ophthalmologists. Surprisingly, I was ranked number 1.

1966

James S. Gordon

My work with population-wide war trauma in the Middle East is, in spite of ongoing conflict, ever more satisfying. The Center for Mind-Body Medicine in Washington, DC, which I founded and direct, completed a study showing that our model of self-care and small-group support reduces psychological trauma by more than 80 percent in Gaza adults. Our results were published in August in the American Psychological Association journal *Traumatology*. A segment on CBS's *60 Minutes*, which aired in 2015, featured our work with war-traumatized children in Gaza and Israel; it was nominated for an Emmy Award. You can see the show and read more about our work in the United States as well as around the world at www.cmbm.org.

I welcome correspondence from HMS graduates interested in learning more and/or collaborating.

1940s

1940

Carl M. McCandless Jr.
November 12, 2016

1944

Anthony P. Caputi
November 28, 2016

1945

Thomas W. Morgan
November 2, 2016

1947

Bruce M. Fisher
October 18, 2016

1948

William M. McCarty
December 5, 2016

1949

Ralph W. Jacobs
November 12, 2016

1950s

1951

Arthur J. Cain
December 29, 2016

1952

H. Brownell Wheeler
November 22, 2016

1954

James E. Boyett
August 2, 2016

Howard A. Pearson
October 16, 2016

1955

R. Kenneth Kenigsberg
September 27, 2016

1956

William E. Korndorffer Jr.
April 25, 2016

1960s

1962

Charles S. August
September 15, 2016

1965

Walter A. Reiling Jr.
October 25, 2016

Richard H. Seder
December 19, 2016

1980s

1981

David Bruce Rogers
December 8, 2016

1990s

1999

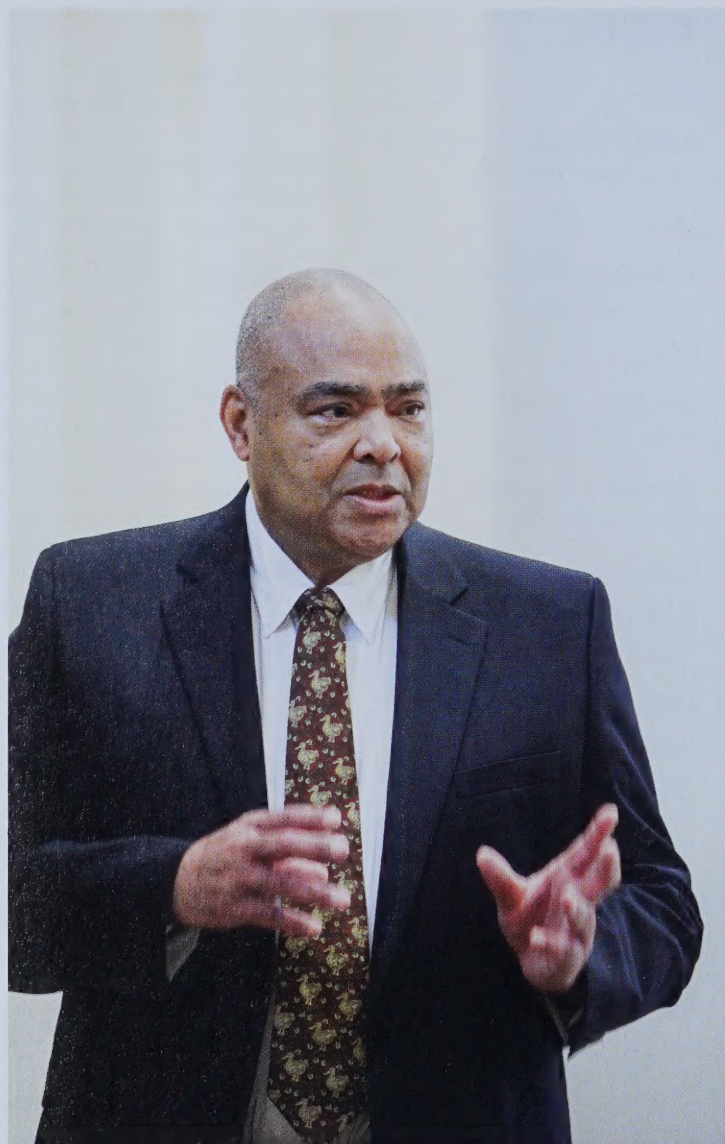
Kamala D. Dansinghani
October 14, 2016

This listing of deceased alumni includes those whose notices of death were received between October 11, 2016, and February 10, 2017. Links to full obituaries of these alumni can be found at hms.harvard.edu/memorial.

If you know of an HMS alumna/us who has died recently, please email the link to the obituary to hmsalum@hms.harvard.edu.

TAKING A HISTORY

PROFILE OF EDGAR MILFORD, CLASS OF 1971



CLAIMS TO FAME

Associate professor of medicine, Harvard Medical School; director of the Tissue Typing Laboratory, Brigham and Women's Hospital and Dana-Farber Cancer Institute; transplant nephrologist and senior physician, Division of Renal (Kidney) Medicine, Brigham and Women's; adviser on stem cell transplantation and solid organ transplantation to the U.S.

Secretary for Health and Human Services, 2013–15, with another term beginning in 2017.

WELL-GROUNDED

"There was no entertainment, so we would always just go outside," says Edgar Milford, explaining why, early in life, he immersed himself in nature. Milford's childhood was filled with camping trips and walks in the forest near his home

in Nanuet, New York. Because his family grew the food they ate—and, perhaps, because his mother, an elementary-school teacher, had an educator's urge to instruct—Milford learned about animals, plants, and gardening. In addition, Milford was tutored in botany and entomology by an octogenarian neighbor who was one of the first to earn a degree in Cornell University's graduate program in botany.

"She took me under her wing," he says.

Acceptance to the Bronx High School of Science meant Milford had to uproot himself and move to New York City, where, for a short time, he lived in his uncle's home in Harlem. The city, however, was not for him. Soon, he traded urban living for a daily five-hour train commute, just to return to the land he loved.

THE PATH TAKEN

While in high school, Milford accrued so many college credits that he was able to start at Harvard College as a sophomore. A major in biochemical sciences and various research projects on DNA set the stage for his applying to medical school. His acceptance to HMS meant that he would not only become a doctor, but that he would follow the career path of his father, a physician who had immigrated to this country from Haiti.

Once in medical school, Milford set out to learn what he could about medicine, in class and in life. When he had lived in Harlem, he had witnessed the poor health care available to residents there. Inspired by that experience and the social justice movements of the 1960s, Milford elected to work at a free health clinic in Roxbury, Massachusetts. There, he saw how the absence of primary care could undercut a community.

As he applied for residency positions, Milford knew he would look for one that would provide him an immersive experience in a Black community. He matched for a residency at Harlem Hospital Center, which was affiliated with Columbia University College of Physicians and Surgeons.

PLANTING THE SEED

At the time Milford was a resident, "dialysis was in its infancy," he says. Harlem Hospital had only two dialysis machines. Triaging the patients for treatment was a continual problem.

"Many people were dying, including young patients in their twenties," he says. "The incidence of end-stage kidney disease was about three times higher in the Harlem community than in suburban white communities."

Milford developed a deep interest in nephrology and ultimately trained to become a transplant nephrologist. Today, as the head of the Tissue Typing Laboratory at Brigham and Women's, he's responsible for monitoring kidney-disease patients after their transplants as well as overseeing all the genetic testing for the stem cell transplantation program at the Dana-Farber Cancer Institute.

LEAVE ONLY FOOTPRINTS

When he's not working at the hospital, Milford is renewing his passion for the natural world. Woodland hikes now include photography, particularly macrophotography, which allows a close-up perspective of small objects. He has also experimented with using drones to photograph natural areas that are hard to access.

"I love looking at all of the beautiful things that you might not otherwise notice," he says.

—Katie DuBoff



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"I've had the opportunity to watch students mature into great physicians, community leaders, and researchers. My gratification comes from seeing their success."

— Ronald A. Arky, MD

*Daniel D. Federman Distinguished
Professor of Medicine
and Medical Education*

WHAT WILL BE YOUR LEGACY?

Ron Arky is an institution at HMS. His most recent gift—a \$1 million irrevocable bequest—establishes the Arky Family Associate Director and Advisor of the Francis Weld Peabody Society, which he led for nearly three decades.

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